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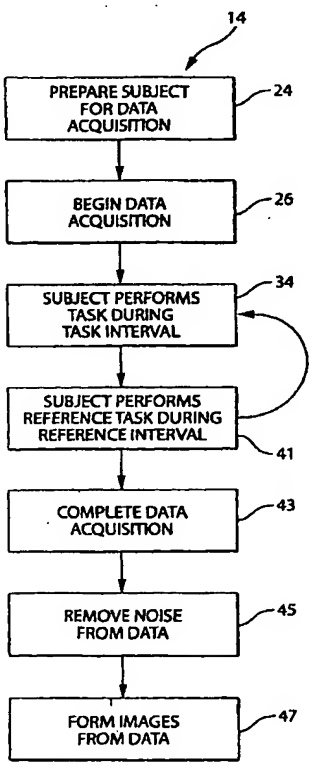

(57) Abstract: The invention relates in some aspects to methods of using functional connectivity brain mapping to assess predictive markers of selecting therapeutic agents, therapies, and/or treatment regimens based on predictive markers of CNS diseases that are determined using functional connectivity brain mapping. The methods of the invention are also useful for predicting whether a subject will or will not respond to a particular therapeutic agent or therapy.

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Exhibit 1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

FUNCTIONAL BRAIN MRI MAPPING AS A MARKER IN CNS DISEASES AND DISORDERS

Related Applications

This application claims priority under 35 U.S.C. §119 from U.S. provisional application serial number 60/664,047, filed March 22, 2005, the entire content of which is incorporated by reference herein in its entirety.

Field of the Invention

The invention relates in some aspects to methods for identifying and selecting therapeutic treatments based on predictive markers of CNS diseases determined with functional connectivity brain mapping.

Background of the Invention

The process of discovering new drugs for treatment of medical disorders often requires administering hundreds of test compounds to human volunteers. If the test compound relieves the manifestations of the disorder, it is considered to be a candidate drug and subjected to further testing.

For many disorders, the manifestations of the disorder are readily observable. However, in the case of neurological and psychiatric disorders, the manifestations are more difficult to quantify. For example, if one were to give a test compound to a volunteer afflicted with Alzheimer's, one would want to test the effect on that volunteer's short term memory. Each such test is a time-consuming proposition. Adding to this difficulty is the need to test enough volunteers to ensure that the conclusions drawn from these tests merit statistical significance.

Magnetic resonance imaging (MRI) has been utilized to examine brain function in neurological diseases such as Alzheimer's disease (AD). Previous studies have included the use of functional MRI for assessing resting connectivity in the hippocampus as a way to analyze the effect of AD on hippocampal activity and as a means to investigate the affect of pharmaceutical agents on AD (U.S. Patent No. 6,490,472), but such studies have not examined functional connectivity across brain regions and have not included assessments of task-related activity between brain regions of subjects.

Summary of the Invention

We have discovered methods of monitoring and assessing connectivity of brain regions of a subject as a measure of the likelihood that a pharmaceutical agent will be effective for the prevention and/or treatment of a neurological or psychiatric disease or disorder in the subject. The methods include, in some aspects, determining the connectivity of two or more neural network nodes in a subject either while the subject performs a task or while the subject is at rest. The methods allow the evaluation of the connectivity of two or more neural network nodes in the subject and can be used to screen for various diseases simultaneously and can also be used to assess candidate pharmaceutical agents and/or therapies for their ability to treat a neurological or psychiatric disease or disorder. The methods of the invention are also useful to predict whether or not a subject will respond to the administration of a pharmaceutical agent or therapy for the treatment of a neurological or psychiatric disease or disorder and can also be used to select a therapeutic regimen for a subject known to have, suspected of having, or at risk of having a neurological or psychiatric disease or disorder. In addition, the methods of the invention can be used to monitor the response of a subject to a pharmaceutical agent, therapy, and/or a therapeutic regimen for a neurological or psychiatric disease or disorder.

According to one aspect of the invention, methods for assessing the likelihood of a subject to have a therapeutic response to a pharmaceutical agent or therapy are provided. The methods include determining a functional connectivity of two or more neural network nodes in a subject performing a task, wherein the subject is known to have or suspected of having a neurological or psychiatric disease or disorder comparing the functional connectivity of the two or more neural network nodes in the subject to a control functional connectivity of the two or more neural network nodes, and assessing the likelihood that the subject will have a therapeutic response to a pharmaceutical agent or therapy based on the comparison of the test and control functional connectivity of the two or more neural network nodes. In some embodiments, the control functional connectivity is a functional connectivity previously determined in the subject performing the task.

According to another aspect of the invention, methods for selecting a therapeutic regimen for a subject known to have or suspected of having a neurological or psychiatric disease or disorder are provided. The methods include, determining a functional connectivity of two or more neural network nodes in a subject performing a task, comparing the functional

connectivity of the two or more neural network nodes in the subject to a control functional connectivity of the two or more neural network nodes, and selecting a therapeutic regimen for the subject based on the comparison of the test and control functional connectivity of the two or more neural network nodes. In certain embodiments, the therapeutic regimen includes administering a pharmaceutical agent or therapy.

According to yet another aspect of the invention, methods for identifying the onset, progression, or regression of a neurological or psychiatric disease or disorder in a subject are provided. The methods included determining a first functional connectivity of two or more neural network nodes in a subject performing a task, determining a second functional connectivity of two or more neural network nodes in the subject performing the task at a time later than the determination of the first functional connectivity of the two or more neural network nodes in the subject performing the task, and comparing the first functional connectivity of the two or more neural network nodes to the second functional connectivity of the two or more neural network nodes, wherein a difference between the first and second functional connectivity of the two or more neural network nodes identifies the onset, progression, or regression of the neurological or psychiatric disease or disorder in the subject. In some embodiments, an increase or decrease in the second functional connectivity of the two or more neural network nodes compared to the first functional connectivity of the two or more neural network nodes indicates the onset or progression of the neurological or psychiatric disease or disorder in the subject. In some embodiments, an increase or decrease in the second functional connectivity of the two or more neural network nodes compared to the first functional connectivity of the two or more neural network nodes indicates the regression of the neurological or psychiatric disease or disorder in the subject.

According to another aspect of the invention, methods for identifying a candidate pharmaceutical agent or therapy for preventing or treating a neurological or psychiatric disorder are provided. The methods include determining a first functional connectivity of two or more neural network nodes in a subject performing a task, wherein the subject has a neurological or psychiatric disease or disorder, administering a candidate pharmaceutical agent or therapy to the subject, determining after the administration of the candidate pharmaceutical agent or therapy a second functional connectivity of the two or more neural network nodes in the subject performing the task, and comparing the first and second functional connectivity of the two or more neural network nodes in the subject, wherein a difference between the first and second functional connectivity of the two or more neural

networks nodes in the subject identifies the candidate pharmaceutical agent or therapy for preventing or treating the neurological or psychiatric disease or disorder. In some embodiments, the difference is an increase in the second functional connectivity of the two or more neural network nodes in the subject compared to the first functional connectivity of the two or more neural network nodes.

In certain embodiments of any of the foregoing aspects of the invention, the control functional connectivity is the functional connectivity in a control subject performing the task. In some embodiments of any of the foregoing aspects of the invention, the control subject does not have the neurological or psychiatric disease or disorder. In some embodiments of any of the foregoing aspects of the invention, the control subject has the neurological or psychiatric disease or disorder. In some embodiments of any of the foregoing aspects of the invention, the neurological or psychiatric disease or disorder is Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, dementia unspecified, multiple sclerosis, depression, anxiety, obsessive compulsive disorder, brain injury, schizophrenia, a sensory neuropathy, a motor neuropathy, a psychotic disorder, migraine, epilepsy, tremor, an affective disorder, stroke, or stroke recovery. In certain embodiments of any of the foregoing aspects of the invention, the neurological or psychiatric disease or disorder is Alzheimer's disease. In some embodiments of any of the foregoing aspects of the invention, the two or more neural network nodes are located in the left dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), and/or medial frontal cortex (MFC). In some embodiments any of the foregoing aspects of the invention, a neural network node is a control neural network node. In certain embodiments of any of the foregoing aspects of the invention, the control neural network node is in the occipitotemporal cortex (OT). In some embodiments of any of the foregoing aspects of the invention, the task includes an N-back task. In some embodiments of any of the foregoing aspects of the invention, the task includes a cognitive task. In some embodiments, of any of the foregoing aspects of the invention, the cognitive task includes a semantic reasoning task or a visuospatial recognition task. In certain embodiments of any of the foregoing aspects of the invention, the task includes a motor task. In some embodiments of any of the foregoing aspects of the invention, the task includes a sensory task. In some embodiments of any of the foregoing aspects of the invention, the task is a self-paced task or an externally paced task. In some embodiments of any of the foregoing aspects of the invention, the method of determining the functional connectivity of two or more neural network nodes in the subject includes obtaining a sequence of functional

magnetic resonance (fMRI) images of the subject during performance of the task. In some embodiments of any of the foregoing aspects of the invention, the method of determining the functional connectivity of two or more neural network nodes in the subject includes collecting task data indicative of functional connectivity of two or more neural network nodes during performance of the task; and filtering, from the task data, a contribution to the task data arising from background neural activity. In certain embodiments of any of the foregoing aspects of the invention, the background neural activity includes neural activity associated with performance of a reference task. In some embodiments of any of the foregoing aspects of the invention, the background neural activity includes neural activity associated with a selected brain region of the subject. In some embodiments of any of the foregoing aspects of the invention, the selected brain region is a region outside the neural network nodes. In some embodiments of any of the foregoing aspects of the invention, the background neural activity includes neural activity associated with the selected region during performance of the task. In some embodiments of any of the foregoing aspects of the invention, determining the functional connectivity of two or more neural network nodes includes having the subject perform the task during a first plurality of task intervals, each having at least a first time segment and a second time segment, collecting data from each of the first time segments into a first data set, collecting data from each of the second time segments into a second data set; and filtering, from the first and second data sets, a contribution to the first and second data sets arising from background neural activity. In certain embodiments of any of the foregoing aspects of the invention, filtering includes performing a correlation between data representative of the background neural activity and the first and second data sets. In some embodiments of any of the foregoing aspects of the invention, filtering includes performing a statistical test between data representative of the background neural activity and the first and second data sets. In some embodiments of any of the foregoing aspects of the invention, the pharmaceutical agent or therapy is for the treatment of the neurological or psychiatric disease or disorder. In some embodiments of any of the foregoing aspects of the invention, the pharmaceutical agent is a selective serotonin reuptake inhibitor (SSRI)/antidepressant, a psychostimulant, an N-methyl-D-asparate (NMDA) receptor modulator, an antipsychotic, an anxiolytic, a dopamine/dopaminergic agent, an immune-modulating agent, a cholinesterase inhibitor, or a GABAergic agent. In some embodiments of any of the foregoing aspects of the invention, the cholinesterase inhibitor is galantamine. In some embodiments of any of the foregoing aspects of the invention, the therapy includes application of a medical device or

brain surgery. In some embodiments of any of the foregoing aspects of the invention, the medical device is deep brain stimulation, vagus nerve stimulation, or transcranial magnetic stimulation.

According to another aspect of the invention, methods for assessing the likelihood of a subject to have a therapeutic response to a pharmaceutical agent or therapy are provided. The methods include determining a resting functional connectivity of two or more neural network nodes in a subject, wherein the subject is known to have or suspected of having a neurological or psychiatric disease or disorder, comparing the resting functional connectivity of the two or more neural network nodes in the subject to a control resting functional connectivity of the two or more neural network nodes, and assessing the likelihood that the subject will have a therapeutic response to a pharmaceutical agent or therapy based on the comparison of the test and control resting functional connectivity of the two or more neural network nodes.

According to yet another aspect of the invention, methods for selecting a therapeutic regimen for a subject known to have or suspected of having a neurological or psychiatric disease or disorder are provided. The methods include determining a resting functional connectivity of two or more neural network nodes in a subject, comparing the resting functional connectivity of the two or more neural network nodes in the subject to a control resting functional connectivity of the two or more neural network nodes, and selecting a therapeutic regimen for the subject based on the comparison of the test and control resting functional connectivity of the two or more neural network nodes.

According to another aspect of the invention, methods for identifying the onset, progression, or regression of a neurological or psychiatric disease or disorder in a subject, are provided. The methods include determining a first resting functional connectivity of two or more neural network nodes in a subject, determining a second resting functional connectivity of two or more neural network nodes the subject at a time later than the determination of the first resting functional connectivity of the two or more neural network nodes in the subject, and comparing the first resting functional connectivity of the two or more neural network nodes to the second resting functional connectivity of the two or more neural network nodes, wherein a difference between the first and second resting functional connectivity of the two or more neural network nodes identifies the onset, progression, or regression of the neurological or psychiatric disease or disorder in the subject. In some embodiments, a decrease in the second resting functional connectivity of the two or more neural network nodes compared to the first resting functional connectivity of the two or more neural network nodes indicates the

onset, progression, or regression of the neurological or psychiatric disease or disorder in the subject. In some embodiments, an increase in the second resting functional connectivity of the two or more neural network nodes compared to the first resting functional connectivity of the two or more neural network nodes indicates the onset, progression, or regression of the neurological or psychiatric disease or disorder in the subject.

According to yet another aspect of the invention, methods for identifying a candidate pharmaceutical agent or therapy for preventing or treating a neurological or psychiatric disorder, are provided. The methods include, determining a first resting functional connectivity of two or more neural network nodes in a subject, wherein the subject has a neurological or psychiatric disease or disorder, administering a candidate pharmaceutical agent to the subject, determining after the administration of the candidate pharmaceutical agent or therapy a second resting functional connectivity of the two or more neural network nodes in the subject, and comparing the first and second resting functional connectivity of the two or more neural network nodes in the subject, wherein a difference between the first and second resting functional connectivity of the two or more neural networks nodes in the subject identifies the candidate pharmaceutical agent or therapy for preventing or treating the neurological or psychiatric disease or disorder. In some embodiments, the difference is an increase in the second resting functional connectivity of the two or more neural network nodes in the subject compared to the first resting functional connectivity of the two or more neural network nodes.

In some embodiments of any of the foregoing aspects of the invention, the control resting functional connectivity is a resting functional connectivity previously determined in the subject. In some embodiments of any of the foregoing aspects of the invention, the control resting functional connectivity is the resting functional connectivity in a control subject. In some embodiments of any of the foregoing aspects of the invention, the control subject does not have the neurological or psychiatric disease or disorder. In some embodiments of any of the foregoing aspects of the invention, the control subject has the neurological or psychiatric disease or disorder. In some embodiments of any of the foregoing aspects of the invention, the neurological or psychiatric disease or disorder is Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, dementia unspecified, multiple sclerosis, depression, anxiety, obsessive compulsive disorder, brain injury, schizophrenia, a sensory neuropathy, a motor neuropathy, a psychotic disorder, migraine, epilepsy, tremor, coma, an affective disorder, stroke, or stroke recovery. In certain

embodiments of any of the foregoing aspects of the invention, the neurological or psychiatric disease or disorder is Alzheimer's disease. In some embodiments of any of the foregoing aspects of the invention, the two or more neural network nodes are located in the left dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), and/or medial frontal cortex (MFC). In some embodiments of any of the foregoing aspects of the invention, a neural network node is a control neural network node. In some embodiments of any of the foregoing aspects of the invention, the control neural network node is in the occipitotemporal cortex (OT). In some embodiments of any of the foregoing aspects of the invention, the method of determining the resting functional connectivity of two or more neural network nodes in the subject includes obtaining a resting sequence of functional magnetic resonance (fMRI) images of the subject. In some embodiments of any of the foregoing aspects of the invention, the method of determining the resting functional connectivity of two or more neural network nodes in the subject includes collecting data indicative of resting functional connectivity of two or more neural network nodes; and filtering, from the data, a contribution to the data arising from background neural activity. In some embodiments of any of the foregoing aspects of the invention, the background neural activity includes neural activity associated with a selected brain region of the subject. In some embodiments of any of the foregoing aspects of the invention, wherein the selected brain region is a region outside the neural network nodes. In some embodiments of any of the foregoing aspects of the invention, determining the resting functional connectivity of two or more neural network nodes includes collecting data from the subject during each of a first plurality of intervals, each having at least a first time segment and a second time segment, wherein data is collected from each of the first time segments into a first data set, and data is collected from each of the second time segments into a second data set, and filtering, from the first and second data sets, a contribution to the first and second data sets arising from background neural activity. In some embodiments of any of the foregoing aspects of the invention, filtering includes performing a correlation between data representative of the background neural activity and the first and second data sets. In some embodiments of any of the foregoing aspects of the invention, filtering includes performing a statistical test between data representative of the background neural activity and the first and second data sets. In some embodiments of any of the foregoing aspects of the invention, the pharmaceutical agent or therapy is for the treatment of the neurological or psychiatric disease or disorder. In some embodiments of any of the foregoing aspects of the invention, the pharmaceutical agent is a selective serotonin reuptake

inhibitor (SSRI)/antidepressant, a psychostimulant, an N-methyl-D-asparate (NMDA) receptor modulator, an antipsychotic, an anxiolytic, a dopamine/dopaminergic agent, an immune-modulating agent, a cholinesterase inhibitor, or a GABAergic agent. In some embodiments of any of the foregoing aspects of the invention, the cholinesterase inhibitor is galantamine. In some embodiments of any of the foregoing aspects of the invention, the therapy includes application of a medical device or brain surgery. In some embodiments of any of the foregoing aspects of the invention, the medical device is deep brain stimulation, vagus nerve stimulation, or transcranial magnetic stimulation.

The invention also includes systems having an imaging system and a data processing system configured to carry out the method recited above.

These and other aspects of the invention will be described in further detail in connection with the detailed description of the invention

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention relates. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

Brief Description of the Figures

Fig. 1 is a flow chart of the process for observing functional connectivity between neural network nodes.

Fig. 2 is a diagram illustrating task intervals and sub-intervals. (Note in a "resting" determination, the task interval may be a rest interval).

Fig. 3 is a signal-flow diagram showing statistical operations carried out on data collected through the method shown in Fig. 1.

Fig. 4 is a digital image of Alzheimer's disease regression maps generated with fMRI of pre-treatment 1-back working memory (WM) ($p<.05$).

Fig. 5 is a series of graphs and brain-scan images from pre-treatment fMRI functional connectivity studies showing activations are correlated with medial frontal cortex activity. Fig. 5 A shows control results, Fig. 5B shows AD responder results, and Fig. 5C shows AD non-responder results.

Fig. 6 is a diagram showing pre-treatment fMRI functional connectivity results for four regions of the brain, MF, DLPFC, PPC and OT. Fig. 6A shows functional connectivity results in subjects that are normal controls. Fig. 6B shows functional connectivity results in subjects that have Alzheimer's disease and are responders to the galantamine treatment. Fig. 6C shows functional connectivity results in subjects that have Alzheimer's disease and are not responders to the galatamine treatment.

Fig. 7 is a diagram showing symbols used in a visuospatial processing task.

Detailed Description of the Invention

We have discovered methods for assessing the functional connectivity of two or more neural network nodes in a subject either while a subject performs a task or while the subject is at rest. The methods of the invention are useful to predict whether or not a subject will respond to the administration of a pharmaceutical agent or therapy for the treatment of a neurological or psychiatric disease or disorder. The methods allow the rapid and reproducible evaluation of the functional connectivity of neural network nodes in a subject and can also be used to screen for drugs and/or therapies that can be used to prevent and/or treat a neurological or psychiatric disease or disorder.

Research in the field of neuroscience has established that the brain utilizes electrical signals to process information and to communicate between adjacent and non-adjacent brain regions. It is known in the art that complex patterns of connections between brain regions exist and the mapping of connections has demonstrated that there is functional connectivity and communication between numerous specific brain regions. Examination of communication within the brain has demonstrated that neurological or psychiatric diseases or disorders can alter the functional connectivity between brain regions.

The functional anatomy of the brain has been extensively examined in the art and there are well-established principles of functional and anatomical organization in the brain. Major brain regions include structures such as the medulla, the pons, the midbrain, the diencephalon, and the cerebral hemispheres. The major brain regions are further recognized by those in the art as encompassing smaller brain regions. For example, the diencephalon includes regions such as the thalamus and hypothalamus. Similarly, the cerebral hemispheres can be subdivided into the basal ganglia and the cerebral cortex, the latter of which can be further divided into regions known as frontal, parietal, temporal and occipital lobes, and in turn, these regions can be further subdivided into regions such as the posterior parietal cortex (PPC), the prefrontal cortex, the medial frontal cortex, etc. The delineations of regions of the brain and the functional connections and attributes of the regions are understood by those of ordinary skill in the art. In the present invention, the functional connectivity between brain regions is determined using functional MRI methods.

As used herein, the term "neural network node", also referred to herein as a "node", means at least a part of an art-recognized region of the brain. A neural network node may be located in the frontal cortex, the posterior parietal cortex, the thalamus, or the midbrain, etc. For example a node may be in (e.g. part of) the posterior parietal cortex (PPC) and thus be part of the PPC, but need not be the entire PPC. The methods of the invention that relate to determining the functional connectivity of two or more neural network nodes allow the determination of functional connectivity of two locations in the brain that are spatially distinct from each other. In some embodiments, two or more neural nodes are in different brain regions and in other embodiments, two or more neural nodes may be in the same brain region.

Neurological and psychiatric diseases and disorders may result in plasticity or remodeling of a brain's functional connections, the occurrence of which may be indicated by alterations in functional connectivity between various brain regions. As used herein, the terms "altered" or "alteration" mean either increased or decreased from normal. For example, the existence and/or level of functional connectivity between two nodes may be normal in a subject who does not have a neurological or psychiatric disease or disorder but that level of functional connectivity may change in the subject as the subject develops a neurological or psychiatric disease or disorder or as the disease or disorder progresses or regresses.

A disease or disorder may be identified by decreased functional connectivity between some neural network nodes and/or increased functional connectivity between other neural network nodes. Additionally, different stages of a disease or disorder may also exhibit

increased functional connectivity between some regions and decreased functional connectivity between other regions. For example, in a subject with AD, the loss of some functional connectivity between two neural network nodes may be associated with a gain of functional connectivity between two other neural network nodes. Although not wishing to be bound by any particular theory, this may offset a functional loss caused by the decrease in functional connectivity, in part or entirely, and may represent a compensation mechanism that the brain utilizes in AD or other neurological or psychiatric diseases or disorders. Thus, for example, a normal subject may be determined to have functional connectivity between nodes 1 and 2, but not nodes 2 and 3, but the onset of AD in the subject may result in the reduction in the connectivity between nodes 1 and 2 and a new or increased connectivity between nodes 1 and 3. Thus, the onset or progression of a neurological or psychiatric disease or disorder may result in a decrease of connectivity of some neural network nodes and an increase in connectivity of other neural network nodes. Similarly, the regression of a neurological or psychiatric disease or disorder may result in the increase in the connectivity of some neural network nodes and may result in the decrease in the connectivity of other neural network nodes of the subject.

Subjects useful in the methods of the invention include humans and non-human primates as well as other mammals such as cats, dogs, sheep, pigs, rodents such as mice, hamsters, and rats. Humans are the most preferred subject for use in the methods of the invention. The methods of the invention are useful to assess neurological and/or psychiatric diseases or disorders in a subject. Examples of neurological or psychiatric disease and disorders, though not intended to be limiting, include Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, dementia unspecified, multiple sclerosis, depression, anxiety, obsessive compulsive disorder, brain injury, schizophrenia, a sensory neuropathy, a motor neuropathy, a psychotic disorder, migraine, epilepsy, tremor, an affective disorder, stroke, or stroke recovery. Those of ordinary skill in the art will recognize that the methods of the invention can also be used to assess additional neurological or psychiatric diseases and disorders and their prevention and treatment agents and strategies.

In some embodiments, a subject is known to have or is suspected of having a neurological or psychiatric disease or disorder. By "known to have" it is meant that a subject has been diagnosed with a disease or disorder. A diagnosis may also include a determination of the status or stage of the disease or disorder in the subject. In some embodiments, a subject is "suspected of having" a neurological or psychiatric disease or disorder, which

means that a formal diagnosis has not been made but one of skill in the art, such a health care professional, believes the subject may have the disease or disorder. Methods for identifying subjects suspected of having a neurological or psychiatric disease or disorder may include genetic testing, behavioral assessment, cognitive assessments, subject's family medical history, subject's medical history, or imaging technologies. Such methods for identifying subjects suspected of having neurological or psychiatric diseases or disorders are well known to those of skill in the medical arts. As used herein, the phrase "suspected of having a neurological or psychiatric disease or disorder" means a subject believed by one of ordinary skill in the medical arts to have the neurological or psychiatric disease or disorder.

In some embodiments, a subject is a control subject. Functional connectivity of two or more neural network nodes in a subject is preferentially compared to a functional connectivity of a control node outside the known neural network. The control may be a predetermined value, which can take a variety of forms. It can be a single value, such as a median or mean. A control value can be established based upon comparative groups (e.g. subjects with the same neurological or psychiatric disease or disorder). These types of control values can serve as control values for subjects who are treated with a candidate pharmaceutical agent or are treated with an art recognized pharmaceutical agent for a disease or disorder. For example, a control for a subject with a neurological or psychiatric disease or disorder may be a determination made in the same subject at a previous time, e.g. a functional connectivity that was previously determined in the subject, or may be a determination made in a different subject, e.g. a control subject. In some embodiments, a control may be the functional connectivity of two or more neural network nodes or brain regions in an individual who is free of a neurological or psychiatric disease or disorder. Thus, a control may be the functional connectivity in a "normal" subject. In some embodiments, a control may be the functional connectivity in a subject before treatment with a pharmaceutical agent or therapy (e.g. to compare functional connectivity before and after treatment).

In some embodiments of the invention, a control determination of functional connectivity of two or more neural network nodes is determined in subject without a neurological or psychiatric disease or disorder. Subjects without a neurological or psychiatric disease or disorder are also referred to herein as "healthy" or "normal" or "neurological or psychiatric disease- and disorder-free" subjects. In some embodiments, a control level of functional connectivity may be a functional connectivity that is compared to a subsequent functional connectivity determination from the same subject. Thus, a control level may be an

initial or starting level of functional connectivity in a subject, and this control level of functional connectivity can be used as a baseline to functional connectivity of the neural network nodes of the subject over time or in response to therapy. For example, the functional connectivity of two or more neural network nodes in a subject following treatment for a neurological or psychiatric disease or disorder can be compared to the starting determination of functional connectivity of the two or more neural network nodes in the subject prior to treatment, or in a subject that was not treated. Such a comparison allows identification of disease or disorder-associated changes and/or changes in status (e.g. stage) of the neurological or psychiatric disease or disorder and also permits the determination of the efficacy of a treatment of the neurological or psychiatric disease or disorder in the subject.

Individuals who may be tested using the methods of the invention may include, as described above herein, subjects known to have, or suspected of having a neurological or psychiatric disease or disorder. Additionally, subjects with a neurological or psychiatric disease or disorder and subjects without a neurological or psychiatric disease or disorder can be compared for the level or presence of functional connectivity of two or more neural network nodes. Other comparative groups or individuals can be subjects with a family history of a disease or disorder and a group without such a family history. Another group of subjects that can be used in the methods of the invention are subjects who have been treated for a neurological or psychiatric disease or disorder.

A predetermined control value of course, will depend upon the particular population of subjects selected. For example, an apparently healthy subject population will have a different 'normal' range of functional connectivity of brain regions than will a population that is known to have a neurological or psychiatric disease or disorder. Accordingly, the predetermined value selected may take into account the category in which a test subject or control subject falls. Appropriate ranges and categories can be selected with no more than routine experimentation by those of ordinary skill in the art. An "abnormal functional connectivity" is a functional connectivity of two or more neural network nodes that is statistically significantly different relative to a selected control.

In addition to connectivity determinations in control subjects, the invention also include determinations of connectivity in regions of the brain that are control regions or reference regions. In some embodiments, a neural network node is a control neural network node. As used herein, a "control neural network node" is a neural network node that is outside of the two or more neural network nodes that are the regions of interest (ROI) being

examined for functional connectivity. Such a control region is a region that may be selected for connectivity measurement based on the expectation that the region maintains "normal" functional connectivity in the subject even if the subject has a neurological or psychiatric disease or disorder. An example of a control neural network node that can be used in the assessment of AD functional connectivity, although not intended to be limiting, is a neural network node located in the occipitotemporal cortex (OT). The determination of functional connectivity in the OT can serve as an internal control for functional connectivity within a subject. One of ordinary skill in the art will recognize that other control neural network nodes may be selected and that selection of an appropriate control neural network node for a disease or disorder can be made based on the pathological and/or clinical characteristics of a particular disorder. Thus, one of ordinary skill in the art can select a control neural network node based on the characteristic of a subject's disease or disorder or based on the existing status of brain connectivity in the subject under study.

The methods of the invention, include, in part determining the functional connectivity of two or more neural network nodes in a subject. The method of determining the functional connectivity may include using imaging methods to obtain a sequence of images of brain regions – e.g. neural network nodes, of the subject. The methods of the invention include, in part, the use of functional MRI (fMRI) methods to determine functional connectivity between brain regions in a subject. As used herein, the term "functional connectivity" means interactive communication (e.g. information passage) between brain regions or nodes. Functional connectivity may be one-way or two-way communication between two or more brain regions or nodes and also includes synchronous node behavior and/or harmonized node behavior. The communication activity may be continuous or may be intermittent and may reflect task-induced activity or may be resting activity. One of ordinary skill in the art will recognize that different regions of the brain are affected in different neurological or psychiatric diseases or disorders, thus, the methods of the invention can be optimized to detect connectivity of regions that are known to be affected in a specific neurological or psychiatric disease or disorder of a subject. An example of connectivity of neural network nodes that is altered in a neurological disease, although not intended to be limiting, is the functional connectivity between brain regions such as the left dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), and medial frontal cortex (MFC), which may be altered in subjects with Alzheimer's disease (AD). Although in some embodiments of the invention, the methods of the invention are described with respect to their use to assess

functional connectivity in subjects with AD, AD is presented as an exemplary disease and one of ordinary skill will recognize that the claimed methods are also useful for the assessment of other neurological or psychiatric diseases or disorders.

The methods of the invention include brain imaging for the determination of functional connectivity. Imaging can be accomplished by a variety of image acquisition systems, for example, MRI ("magnetic resonance imaging") systems, PET ("positron emission tomography") scanners, quantitative electro-encephalography ("QEEG") or magneto-encephalography ("QMEG") systems. Thus, preparation for imaging can include having the subject's head enter the field of an imaging machine, injecting a radioactive tracer into the subject and appropriately positioning the subject within a PET scanner, or attaching electrodes and/or pick-up coils to appropriate areas of the subject's scalp.

Because of the difference between the paramagnetic properties of oxygenated blood and deoxygenated blood, MRI systems are particularly useful for image acquisition. Whole brain blood oxygenation level-dependent (BOLD) fMRI is an MRI method that is known in the art and is useful in the methods of the invention. The acquisition of multiple MRI images of the same region separated in time is referred to as "functional MRI" or "fMRI." Those of ordinary skill in the art will recognize that other methods of imaging the brain and neural network nodes may also be used in the methods of the invention. The following and the procedure outlined in Fig. 1 provide a general description of the imaging aspects of the invention, but are not intended to be limiting.

Once a subject is prepared for the imaging process, the image acquisition system begins acquiring a sequence of data sets during a testing period. As shown in Fig 2, a testing period 28 is divided into one or more task intervals (or task-free intervals if it resting connectivity is being imaged) 30 separated from each other by reference intervals 32. Although the task intervals 30 in Fig. 2 are shown as being the same length as the reference intervals 32, this need not be the case. Referring again to Fig. 1, during the task intervals 30, the subject is asked to perform a task (step 34). Depending on the nature of the disorder and the portion of the brain in which neural activity is to be stimulated, the task can be a motor task, or any of a variety of cognitive tasks. For example, if the disorder is one that affects short-term memory, such as Alzheimer's disease, the task would be one that is expected to exercise that memory. An example of such a task is the 2-back test in which a subject is presented with a stream of symbols and asked to determine whether a current symbol matches the symbol that preceded the preceding symbol. For disorders of the visuospatial processing

system, the test subject is asked to perform tasks that test the recognition of symbols or the identification of missing symbols from a set of symbols. For disorders of the brain's semantic processing system, the test subject is asked to perform simple reasoning tasks such as recognizing a presented word, retrieving from memory an association between that word and a category, and performing a function indicative of recognition of such an association.

Referring again to Fig. 2, each task interval 30 is divided into a number of time segments 36A-D. During each time segment 36A-D, the image acquisition system collects a task data set 35 *TDu,* where the index *i* refers to the task interval 30 and the index *j* identifies the time segment 36A-D within the task interval 30. Data sets (e.g. Task data sets TD_{1i}, TD_{2i} .TD_{Nj},) from corresponding time segments will later be combined to form one image that shows neural activity during a selected time interval following initiation of the task. For example, each task interval 30 will have a first time segment 36A, a second time segment 36B, and a last time segment 36D.

As shown in Fig. 3, the task data sets TD_{ij} for first time segments of each task interval 30 will be averaged together, with the resulting time segment average 37 to be used in constructing a first image 38 in the sequence of images 40. Task data sets TD_{2}~ for second time segments of each task interval 30 will likewise be averaged together, with the resulting time segment average 42 being used in constructing the next image 44 in the sequence of images 40.

As the number of time segments 36 per task interval 30 increases, the temporal resolution with which the evolution of neural activity can be viewed also increases. On the other hand, as the number of time segments 36 increases, each time segment 36 becomes proportionately shorter. Hence the amount of data that can be gathered during any one time segment 36 decreases. It will therefore be necessary to have more task intervals 30, and hence a longer test period 28, to maintain the overall quality of the resulting images.

While the test subject performs the selected task, a great deal of background neural activity that is not associated with performance of that task continues to take place. Since it is only the neural activity associated with performance of the task that is ultimately of interest, it is desirable to filter out as much non-task related neural activity as possible.

Referring again to Fig. 2, reference data sets 39 (RD_1) acquired during reference intervals 32 provide a basis for filtering non-task related neural activity. Since the task is not being performed during the reference intervals 32, neural activity during the reference interval 32 provides an indication of background neural activity whose statistical effects on task data

sets 35 can later be removed. Because the reference data set 39 is intended to represent constant background neural activity, there is no advantage to dividing the reference interval 32 into time segments and collecting reference data sets 39 in each such time segment. Consequently, there is generally only one reference data set 39 per reference interval 32. During the reference interval 32, the subject is asked to perform a reference task (see Fig. 1, step 41). This process is repeated, with the subject performing tasks during the task interval (step 34) and performing a reference task (step 41) during the reference interval 32, until the completion of data acquisition (step 43). The remaining steps in the new method are to remove the noise from the data (step 45) and to form images therefrom (step 47).

Referring again to Fig. 3, the reference data sets 39 are likewise averaged together. The resulting reference average 46 is statistically combined with each of the four time segment averages 37, 42, 48, 50 to extract only that data that represents neurological activity associated with performing the task. A variety of known statistical techniques are available for achieving this result. For example, one can perform a cross-correlation or T-test between the time segment averages and the reference average. Or, one can perform multiple regression analysis or any one of a variety of non-parametric statistical procedures to achieve this same goal. In addition, for each image 38, 44, 52, 54 in the image sequence 40, one might simply evaluate differences between the reference average 46 and the time segment average 37, 42, 48, 50 for that image 38, 44, 52, 54.

It will be understood by those of skill in the art that the testing and data acquisition methods for a non-task-based determination, e.g. determination of resting functional connectivity, may be performed in a manner similar to that described for the task-based testing and data acquisition except that no task is performed during the "task" periods. Thus, a similar process as that provided above herein for the collection of task activity data can be used for the acquisition of resting activity data by replacing the "task" periods with rest periods of data collection.

The ability to assess functional connectivity in a subject during a task and at rest, allows the methods described herein to be used in subjects whose abilities decline as a result of neurological or psychiatric disease or disorder. For example, the methods of the invention can be used to assess functional connectivity in a subject during task performance and at rest, and if the subject subsequently loses the ability for task performance (e.g. due to the onset or progression of a neurological or psychiatric disease or disorder) later determinations of functional connectivity in the subject can be done using resting data collection methods of the

invention, thus allowing the comparison of the initial and later functional connectivity for the subject.

One of ordinary skill will recognize that various statistical methods can be useful to for the analysis of the imaging data. Whichever statistical technique is used, the end result is to distinguish a signal due to task-related activity from a reference signal that, in this case, corresponds to background activity. However, there is no requirement that the reference signal correspond to background activity. For example, in some cases, it may be desirable to identify regions of the brain whose neural activity is correlated with a reference region of the brain. In such a case, the reference signal would be a measure of the time-varying neural activity within the reference region of the brain.

In the case in which the reference signal corresponds to activity in a reference region of the brain, the reference interval 32 is no longer necessary for collecting reference information. However the reference interval 32 may still be necessary to allow the test subject to rest, thereby allowing neural activity to die down so that the task can be always be repeated against the same backdrop of neural activity.

In this case, in which the image sequence 40 shows neural activity that corresponds to neural activity in a reference region of the brain, both reference data sets 39 and task data sets 35 are collected during performance of the task, i.e. during the task interval 36. Data arising from the reference region of the brain is sequestered from data arising from the remainder of the brain and processed as described above in connection with processing the task data sets 35. In effect, the only distinction is that the reference data set 39 no longer represents the generally constant background neural activity present when the test subject is not performing a task. Instead, the reference data set 39 now represents the time-varying neural activity of a selected portion of the brain during performance of the task. The distinction is thus analogous to the difference between determining the trajectory of a moving target relative to a stationary background and determining the trajectory of a moving target relative to a moving object.

In some embodiments, the determination of functional connectivity of two or more neural network nodes may take place while the subject is performing a task and in other embodiments, the determination may be a resting determination that is made when the subject is not performing a task. Examples of tasks that can be performed by a subject during a determination of connectivity of neural network nodes include, but are not limited to: executive-function tasks, N-back tasks, cognitive tasks (e.g. semantic reasoning or

visuospatial tasks), sensory tasks, and motor tasks, etc.

In some embodiments of the invention, a task is an externally paced task, in which the rate or speed at which the subject performs the task is determined by an external source. For example, if a task involves a series of choices and responses to be made by the subject, an externally paced task will proceed through the series at a pace externally set. In other embodiments of the invention, a task is a self-paced task. In a self-paced task the rate or speed at which a subject performs a task is determined by the subject, not an external source.

In some embodiments, the method of determining the functional connectivity of two or more neural network nodes in the subject includes collecting task data indicative of functional connectivity of two or more neural network nodes during performance of the task; and filtering, from the task data, a contribution to the task data arising from background neural activity. Background neural activity may include neural activity associated with performance of a reference task and/or may include neural activity associated with a selected brain region of the subject. In some embodiments, the selected brain region is a region that is not the two or more neural network nodes. In addition, the background neural activity may include neural activity associated with the selected region during performance of the task.

In some task-based assessments of functional connectivity of two or more neural network nodes includes having the subject perform the task during a first plurality of task intervals, each having at least a first time segment and a second time segment, collecting data from each of the first time segments into a first data set, collecting data from each of the second time segments into a second data set; and filtering, from the first and second data sets, a contribution to the first and second data sets arising from background neural activity. Filtering may include performing a correlation between data representative of the background neural activity and the first and second data sets and/or filtering may include performing a statistical test between data representative of the background neural activity and the first and second data sets. As used herein, the term "plurality" means more than 1, 2, 3, 4, 5,6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000.

The invention, in part, includes methods of determining the resting functional connectivity of two or more neural network nodes in a subject. A resting functional connectivity determination is a determination of connectivity in the brain of the subject when the subject is not performing a task – e.g. is at rest. The determination may include collecting data indicative of resting functional connectivity of two or more neural network nodes and the

filtering, from the data, of contributions to the data that come from background neural activity. As used herein, background neural activity includes the baseline activity that is present in the brain that is not associated with the functional connectivity of the neural network regions under examination. Thus, background neural activity may be activity present or produced in brain regions that are not the two or more neural network nodes. For example, the background neural activity may include neural activity that is associated with a selected brain region of the subject, that is not the two or more neural network nodes, thus, the selected brain region is a region outside the neural network nodes. The background neural activity is activity that may be filtered out and removed from the functional connectivity data collected for the regions of interest – e.g. the two or more neural network nodes. Thus, the neural activity values that are determined, e.g. with fMRI measurement of non-neural network nodes are "background noise" that is removed from the fMRI measurements of the functional connectivity of the two or more neural network nodes. The steps of filtering may include performing a correlation between data representative of the background neural activity and the first and second data sets and/or may include performing a statistical test between data representative of the background neural activity and the first and second data sets.

Thus, in some embodiments, the fMRI images collected from a subject are resting images, e.g. non-task associated images that are collected while the subject is at rest. The collection of resting functional connectivity of two or more neural network nodes may include collecting data (e.g. fMRI data) from the subject during each of a first set of multiple (a plurality of) intervals, each having at least a first time segment and a second time segment, wherein data is collected from each of the first time segments into a first data set, and data is collected from each of the second time segments into a second data set, and the contribution to the data that is collected that arises from background neural activity is filtered from the first and second data sets. Thus, the neural activity values that are determined, e.g. with fMRI measurement of non-neural network nodes are "background noise" that is removed from the fMRI measurements of the functional connectivity of the two or more neural network nodes. The steps of filtering may include performing a correlation between data representative of the background neural activity and the first and second data sets and/or may include performing a statistical test between data representative of the background neural activity and the first and second data sets.

Prediction of response

In some embodiments, the methods of the invention may be used determine the connectivity of two or more neural network nodes in a subject with a neurological or psychiatric disease or disorder in a subject and the determination may be used to assess the likelihood or predict whether or not a pharmaceutical agent or therapy useful for the treatment of the disease or disorder, will be effective in that subject. For example, specific reductions or increases in the functional connectivity of two or more neural network nodes may indicate whether a specific pharmaceutical agent or therapy that alters the functional connectivity of the two or more neural network nodes a subject with a neurological or psychiatric disease or disorder will be effective in the subject. For example, the methods of the invention may be used to determine that subjects that respond to a particular pharmaceutical agent or therapy may have a functional connectivity of two or more neural network nodes and subjects that don't respond to the pharmaceutical agent or therapy may not have the same connectivity or level of connectivity of the two or more neural network nodes. Based on determinations of connectivity characteristics of responders and non-responders, the determination of the connectivity of the two or more neural network nodes in a test subject can be the basis for a prediction of whether or not the test subject will respond or not respond to the pharmaceutical agent or therapy.

As used herein, assessing the likelihood that a subject will have a therapeutic response means determining whether it is likely or probable that a subject will respond therapeutically to a pharmaceutical agent or therapy given as a treatment for a neurological or psychiatric disorder or disease. Thus, the methods of the invention can be used to predict whether a subject will respond to a pharmaceutical agent or therapy or not respond to the pharmaceutical agent or therapy for the treatment of a disease or disorder. As used herein, the term "therapeutic response" means a response to an agent or therapy administered for prevention or treatment of a disorder or disease. As used herein, a pharmaceutical agent is a drug or compound that is administered to a subject for the treatment of a disease or disorder. Examples of pharmaceutical agents that can be examined using the methods of the invention, include, but are not limited to: a selective serotonin reuptake inhibitors (SSRI)/antidepressants, psychostimulants, N-methyl-D-asparate (NMDA) receptor modulators, antipsychotics, anxiolytics, dopamine/dopaminergic agents, immune-modulating agents, cholinesterase inhibitors, or GABAergic agents. In some embodiments the cholinesterase inhibitor is galantamine. Those of skill in the art will recognize that numerous other pharmaceutical agents for the prevention or treatment of neurological or psychiatric

diseases or disorders can be tested and assessed using the methods of the invention.

In addition to responses to pharmaceutical agents, the methods of the invention are also useful to a subject's response or likelihood of a response to a therapy. As used herein, the term "therapy" includes procedures or devices that are applied to, administered to, or used on a subject for the prevention or treatment of a disease or disorder. Examples of therapies, although not intended to be limiting include: the use of medical devices (e.g. deep brain stimulation, vagus nerve stimulator, transcranial magnetic stimulation, etc.) or brain surgery (e.g., epilepsy surgery, thalamotomy, pallidotomy, etc.). Those of ordinary skill in the art will recognized that additional procedures can also be used as therapies for neurological or psychiatric diseases or disorders.

Monitoring Onset, Progression, and Regression

The invention is also directed, in part, to the assessment of the status or stage of a neurological or psychiatric disease or disorder and for the evaluation of a subject's response to a treatment.

Different stages of a disease or disorder may exhibit different changes in functional connectivity of brain regions. Some regions may exhibit increased connectivity between some regions and other regions may exhibit decreased connectivity. For example, early-stage AD may include the loss of some connectivity between two neural network nodes but no loss between two other neural network nodes. Thus the determination of the functional connectivity of those neural network nodes may be a marker for the stage of a neurological or psychiatric disease or disorder. Similarly, plasticity may differ at different stages of a neurological or psychiatric disease or disorder thus the gain of connectivity between neural network nodes may be a marker for the stage of the disease. The methods of the invention can be used to compare the functional connectivity of brain regions in a subject as a determination of the status of the disease in the subject. The methods of the invention can thus be used to determine the onset or progression of a neurological or psychiatric disease or disorder that has a decrease of connectivity of some neural network nodes and an increase in connectivity of other neural network nodes. Similarly, the methods of the invention can be used to determine the regression of a neurological or psychiatric disease or disorder that has an increase in the connectivity of some neural network nodes and a decrease in the connectivity of other neural network nodes.

Screening for Pharmaceutical Agents and Therapies

The methods of the invention are also useful for screening for and identifying pharmaceutical agents and/or therapies that alter functional connectivity of neural network nodes. As used herein, the term "agent" can be a molecule or combined molecules (e.g. a complex of two or more molecules in association with each other). A pharmaceutical agent for the treatment or prevention of a neurological or psychiatric disease or disorder may be a compound that alters (e.g. increases and/or decreases) functional connectivity of two or more neural network nodes in a subject. In addition to screening for pharmaceutical agents, the methods of the invention are also useful to screen therapies for the treatment of neurological or psychiatric diseases and disorders. Examples of therapies, although not intended to be limiting include: the use of medical devices, procedures, and/or surgeries. The methods of the invention are also useful to assess combination therapies that may include pharmaceutical agents, devices, procedures, and/or surgeries.

The methods of the invention include imaging-based (*in vivo*) assays of various kinds. Imaging-based assays may include the use of fMRI methods to determine the functional connectivity of neural network nodes. In some embodiments, the methods of the invention include administering to a subject a pharmaceutical agent that is a candidate agent for altering the functional connectivity of neural network nodes. Candidate agents and candidate therapies for altering functional connectivity of neural network nodes can be screened for altering (increasing or decreasing) functional connectivity of neural network nodes using the assays described herein (e.g., in the Examples section).

A subject with a neurological or psychiatric disease or disorder may be tested using the methods of the invention and then administered a candidate pharmaceutical agent or therapy and retested. A comparison of the connectivity of the two or more neural network nodes between the pre and post treatment tests in the subject can be used as an indication of whether the candidate pharmaceutical agent or therapy alters or changes the connectivity of the two or more neural network nodes in a subject and thus, may be a useful agent or therapy to treat the neurological or psychiatric disease or disorder. A "candidate" pharmaceutical agent is a drug or compound that may be useful for the treatment of a disease or disorder. As described herein, the methods of the invention are useful for screening for candidate pharmaceutical agents and/or for testing the efficacy and effect of a candidate pharmaceutical agent as a treatment for a neurological or psychiatric disease or disorder. Similarly, a candidate therapy is a therapy that may be useful for the treatment of a disease or disorder.

As described herein, the methods of the invention are useful for screening for candidate therapies and/or for testing the efficacy and effect of a candidate therapy as a treatment for a neurological or psychiatric disease or disorder.

Generally, the screening methods involve assaying for agents or therapies that alter (increase or decrease) the functional connectivity of two or more neural network nodes, by assessing the effect of the agent or therapy on the functional connectivity of two or more neural network nodes using fMRI methods as described herein. The methods of the invention may be used to assess the effect of a candidate agent or therapy on functional connectivity of two or more neural network nodes.

The candidate agent for altering functional connectivity of two or more neural network nodes that can be used in the assays of the invention can be natural or synthetic compounds, such as those in small molecule libraries of compounds (including compounds derived by combinatorial chemistry). Natural product libraries also can be screened using such methods, as can selected libraries of compounds known to exert pharmacological effects, such as libraries of FDA-approved drugs. Compounds identified by the assays can be used in therapeutic methods of the invention described below.

Candidate agents to alter functional connectivity of two or more neural network nodes may encompass numerous chemical classes, although typically they are organic compounds. In some embodiments, the candidate pharmacological agents are small organic compounds, i.e., those having a molecular weight of more than 50 yet less than about 2500, preferably less than about 1000 and, more preferably, less than about 500. Candidate agents comprise functional chemical groups necessary for structural interactions with proteins and/or nucleic acid molecules, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups and more preferably at least three of the functional chemical groups. The candidate agents can comprise cyclic carbon or heterocyclic structure and/or aromatic or polyaromatic structures substituted with one or more of the above-identified functional groups. Candidate agents also can be biomolecules such as peptides, saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or structural analogs of the above, or combinations thereof and the like. Where the agent is a nucleic acid molecule, the agent typically is a DNA or RNA molecule, although modified nucleic acid molecules as defined herein are also contemplated.

Candidate agents for altering functional connectivity of two or more neural network nodes can be obtained from a wide variety of sources including libraries of synthetic or

natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides, synthetic organic combinatorial libraries, phage display libraries of random peptides, and the like. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural and synthetically produced libraries and compounds can be readily be modified through conventional chemical, physical, and biochemical means. Further, known pharmacological agents can be tested and further may be subjected to directed or random chemical modifications such as acylation, alkylation, esterification, amidification, etc. to produce structural analogs of the agents.

A variety of other reagents also can be included in the assay mixtures of the invention. These include reagents such as salts, buffers, neutral proteins (e.g., albumin), detergents, etc. which may be used to facilitate optimal protein-protein and/or protein-nucleic acid binding. Such a reagent may also reduce non-specific or background interactions of the reaction components. Other reagents that improve the efficiency of the assay such as protease inhibitors, nuclease inhibitors, antimicrobial agents, and the like may also be used.

In general, the mixture of the foregoing assay materials is incubated under conditions whereby, but for the presence of the candidate pharmacological agent, a control level of functional connectivity of two or more neural network nodes will be present. Some functional connectivity altering molecules or compounds will increase functional connectivity of neural network nodes and some will decrease the functional connectivity of neural network nodes, as evidenced by the determination of functional connectivity of two or more neural network nodes using the assays such as those described herein. It will be understood that a decrease or reduction of functional connectivity may mean reduction to zero or may mean reduction to a rate or amount below a normal level, a previous level, or a control level. An increase may be an increase to an amount above a normal level, a previous level, or a control level.

As mentioned above, it is possible to determine the efficacy of a recognized pharmaceutical agent or therapy or a candidate pharmaceutical agent or therapy for a disease or disorder by monitoring changes in the absolute or relative functional connectivity of two or more neural network nodes in the absence and/or presence of a pharmaceutical agent or therapy or candidate pharmaceutical agent or therapy. The functional connectivity of two or more neural network nodes in a subject who has been administered the candidate compound

or therapy, as compared to the functional connectivity of two or more neural network nodes in a subject not administered the candidate compound or therapy, provides an indication of the efficacy of a candidate compound's or therapy's alteration of functional connectivity of two or more neural network nodes in the subject. Accordingly, one can monitor the changes in functional connectivity (e.g. using fMRI) to determine the efficacy of a candidate compound or therapy for altering functional connectivity. Thus, using the assays of the invention, one can identify compounds and/or therapies for use in the prevention and/or treatment of neurological or psychiatric diseases or disorders, which include, but are not limited to: Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, dementia unspecified, multiple sclerosis, depression, anxiety, obsessive compulsive disorder, brain injury, schizophrenia, a sensory neuropathy, a motor neuropathy, a psychotic disorder, migraine, epilepsy, tremor, coma, an affective disorder, stroke, or stroke recovery.

Selecting Therapeutic Regimen

In addition to predicting whether or not a subject will respond to a pharmaceutical agent or therapy for prevention or treatment of a neurological or psychiatric disease or disorder, the methods of the invention can also be used to select a therapeutic regimen for a subject suspected of having or known to have a neurological or psychiatric disease or disorder. Thus, the methods of the invention can be used to determine the functional connectivity of two or more neural network nodes in a subject performing a task or at rest, and the functional connectivity can be compared to a control functional connectivity of the two or more neural network nodes, and based on the comparison, a therapeutic regimen for the subject can be selected.' As used herein, the term "therapeutic regimen" means a treatment for the subject. A therapeutic regimen may include administration of pharmaceutical agents and/or application of a therapy. The selection of the regimen may include selection of dose amount, timing, duration of treatment, combination therapies with other pharmaceutical agents or therapies, and any other aspects of treatment decision making that are used by those of skill in the arts in the treatment of the neurological or psychiatric disease or disorder of the subject. A therapeutic regimen may also include the use of therapies such as procedures or devices that are administered to or used on a subject for the prevention or treatment of a disease or disorder. Examples of therapies, although not intended to be limiting include: the use of medical devices or brain surgery.

The selection of a therapeutic regimen may be based on a determination of the

functional connectivity present in the subject. The determination of the functional connectivity of two or more neural network nodes may indicate that a specific pharmaceutical agent and/or therapy would be beneficial for the subject based on the state of the subject's functional connectivity. For example, a subject may have a functional connectivity of two or more neural network nodes that is similar to a functional connectivity that has been shown to be improved by a therapeutic regimen with a particular pharmaceutical agent and/or therapy and that regimen may be selected for the subject. Following administration of a pharmaceutical agent and/or therapy, the methods of the invention may be used to ascertain the efficacy of the selected treatment regimen in the subject.

In certain embodiments, the method for treating a subject with a neurological or psychiatric disease or disorder involves determining the functional connectivity of two or more neural network nodes in a subject and using that determination as a basis for selecting a candidate pharmaceutical agent and/or therapy and the timing, amount, and delivery regimen for the agent and/or therapy to be administered to the subject. In addition, the methods of the invention can be used to assess the efficacy of a pharmaceutical agent, candidate pharmaceutical agent, therapy, or candidate therapy administered to a subject.

Various techniques may be employed for introducing candidate agents to a subject. In some embodiments, the agents that alter functional connectivity can be agents that are specifically targeted to neural tissues using various delivery methods, including, but not limited to: administration to the brain, attachment of carriers that cross the blood-brain barrier, the addition of targeting molecules to direct the compounds of the invention to neuronal cells and/or tissues. Additional methods to specifically target molecules and compositions of the invention to muscle tissues are known to those of ordinary skill in the art.

In some embodiments of the invention, an agent to alter functional connectivity of two or more neural network nodes may be delivered in the form of a delivery complex. The delivery complex may deliver the agent into any cell type, or may be associated with a molecule for targeting a specific cell type. Examples of delivery complexes include an agent of the invention associated with: a sterol (e.g., cholesterol), a lipid (e.g., a cationic lipid, virosome or liposome), or a target cell specific binding agent (e.g., an antibody, including but not limited to monoclonal antibodies, or a ligand recognized by target cell-specific receptor). Some delivery complexes may be sufficiently stable *in vivo* to prevent significant uncoupling prior to internalization by the target cell. However, the delivery complex can be cleavable under appropriate conditions within the cell so that the compound is released in a functional

form.

An example of a targeting method, although not intended to be limiting, is the use of liposomes to deliver a pharmaceutical agent into a cell. Liposomes may be targeted to a particular tissue, such as neuronal cells, the liposome linked to a specific ligand such as a monoclonal antibody, sugar, glycolipid, or protein. Such proteins include proteins or fragments thereof specific for a particular cell type, antibodies for proteins that undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half life, molecules that transport across the blood brain barrier, and the like.

Liposomes are commercially available from Invitrogen Corporation (Carlsbad, CA), for example, as LIPOFECTIN® and LIPOFECTACE®, which are formed of cationic lipids such as N-[1-(2,3 dioleyloxy)-propyl]-N, N, N-trimethylammonium chloride (DOTMA) and dimethyl dioctadecylammonium bromide (DDAB). Methods for making liposomes are well known in the art and have been described in many publications.

When administered, the pharmaceutical agents (also referred to herein as pharmaceutical compositions and/or pharmaceutical compounds) of the present invention are administered in pharmaceutically acceptable preparations. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic agents. When used in medicine, the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such pharmaceutically-acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic, malonic, succinic, and the like. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts. Preferred components of the composition are described above in conjunction with the description of the pharmacological agents and/or compositions of the invention.

A pharmaceutical agent may be combined, if desired, with a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" as used herein means one or more compatible solid or liquid fillers, diluents or encapsulating substances which are suitable for administration into a human. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the

application. The components of the pharmaceutical compositions also are capable of being co-mingled with the pharmacological agents of the invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy.

The pharmaceutical agents that alter functional connectivity may contain suitable buffering agents, as described above, including: acetate, phosphate, citrate, glycine, borate, carbonate, bicarbonate, hydroxide (and other bases) and pharmaceutically acceptable salts of the foregoing compounds. The pharmaceutical compositions also may contain, optionally, suitable preservatives, such as: benzalkonium chloride; chlorobutanol; parabens and thimerosal.

The therapeutics of the invention can be administered by any conventional route including injection or by gradual infusion over time. Various modes of administration will be known to one of ordinary skill in the art which effectively deliver the pharmacological agents of the invention to a desired tissue, cell, or bodily fluid. The administration methods include: topical, intravenous, oral, inhalation, intracavity, intrathecal, intrasynovial, buccal, intraperitoneal, sublingual, intranasal, transdermal, intravitreal, subcutaneous, intramuscular and intradermal administration. The invention is not limited by the particular modes of administration disclosed herein. Standard references in the art (e.g., Remington: The Science and Practice of Pharmacy, A. R. Gennaro, Editor, 20th edition, 2000) provide modes of administration and formulations for delivery of various pharmaceutical preparations and formulations in pharmaceutical carriers. Other protocols which are useful for the administration of pharmacological agents of the invention will be known to one of ordinary skill in the art, in which the dose amount, schedule of administration, sites of administration, mode of administration (e.g., intra-organ) and the like vary from those presented herein.

The therapeutic compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the compounds into association with a carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the therapeutic agent into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the therapeutic agent, which is preferably isotonic with the blood of the recipient. This aqueous preparation may be formulated according to known methods

using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Carrier formulations suitable for administration of pharmaceutical agents can be found in Remington: The Science and Practice of Pharmacy, A. R. Gennaro, Editor, 20th edition, 2000).

Compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the therapeutic agent. Other compositions include suspensions in aqueous liquors or non-aqueous liquids such as a syrup, an elixir, or an emulsion.

The invention provides a composition of the above-described agents for use as a medicament, methods for preparing the medicament and methods for the sustained release of the medicament *in vivo*. Delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the therapeutic agent of the invention, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer-based systems such as polylactic and polyglycolic acid, poly(lactide-glycolide), copolyoxalates, polyanhydrides, polyesteramides, polyorthoesters, polyhydroxybutyric acid, and polycaprolactone. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Pat. No. 5,075,109. Nonpolymer systems that are lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-, di- and tri-glycerides; phospholipids; hydrogel release systems; silastic systems; peptide based systems; wax coatings, compressed tablets using conventional binders and excipients, partially fused implants and the like. Specific examples include, but are not limited to: (a) erosional systems in which the polysaccharide is contained in a form within a matrix, found in U.S. Patent Nos. 4,452,775, 4,675,189, and 5,736,152, and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Patent Nos. 3,854,480, 5,133,974 and 5,407,686. In

addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

In one particular embodiment, the preferred vehicle is a biocompatible microparticle or implant that is suitable for implantation into the mammalian recipient. Exemplary bioerodible implants that are useful in accordance with this method are described in PCT International application no. PCT/US95/03307 (Publication No. WO 95/24929, entitled "Polymeric Gene Delivery System"). The polymeric matrix is used to achieve sustained release of the therapeutic agent in the subject. In accordance with the instant invention, the compound(s) of the invention is encapsulated or dispersed within a biocompatible, preferably biodegradable polymeric matrix, such as those disclosed in PCT/US95/03307. The polymeric matrix may be in the form of a microparticle such as a microsphere (wherein the compound is dispersed throughout a solid polymeric matrix) or a microcapsule (wherein the compound is stored in the core of a polymeric shell). Other forms of the polymeric matrix for containing the compounds of the invention include films, coatings, gels, implants, and stents. The size and composition of the polymeric matrix device is selected to result in favorable release kinetics in the tissue into which the matrix device is implanted. The size of the polymeric matrix device further is selected according to the method of delivery that is to be used. The polymeric matrix composition can be selected to have both favorable degradation rates and also to be formed of a material that is bioadhesive, to further increase the effectiveness of transfer when the device is administered to a vascular surface. The matrix composition also can be selected not to degrade, but rather, to release by diffusion over an extended period of time.

Both non-biodegradable and biodegradable polymeric matrices can be used to deliver agents of the invention of the invention to the subject. Biodegradable matrices are preferred. Such polymers may be natural or synthetic polymers. Synthetic polymers are preferred. The polymer is selected based on the period of time over which release is desired, generally in the order of a few hours to a year or longer. Typically, release over a period ranging from between a few hours and three to twelve months is most desirable. The polymer optionally is in the form of a hydrogel that can absorb up to about 90% of its weight in water and further, optionally is cross-linked with multi-valent ions or other polymers.

In general, the agents of the invention are delivered using the bioerodible implant by way of diffusion, or more preferably, by degradation of the polymeric matrix. Exemplary synthetic polymers that can be used to form the biodegradable delivery system include:

polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terepthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes and co-polymers thereof, alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, polymers of acrylic and methacrylic esters, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellulose triacetate, cellulose sulphate sodium salt, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyethylene, polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl alcohols), polyvinyl acetate, poly vinyl chloride, polystyrene and polyvinylpyrrolidone.

Examples of non-biodegradable polymers include ethylene vinyl acetate, poly(meth)acrylic acid, polyamides, copolymers and mixtures thereof.

Examples of biodegradable polymers include synthetic polymers such as polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, polyurethanes, poly(butic acid), poly(valeric acid), and poly(lactide-cocaprolactone), and natural polymers such as alginate and other polysaccharides including dextran and cellulose, collagen, chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), albumin and other hydrophilic proteins, zein and other prolamines and hydrophobic proteins, copolymers and mixtures thereof. In general, these materials degrade either by enzymatic hydrolysis or exposure to water *in vivo*, by surface or bulk erosion.

Bioadhesive polymers of particular interest include bioerodible hydrogels described by H. S. Sawhney, C. P. Pathak and J. A. Hubell in *Macromolecules*, 1993:26:581-587, the teachings of which are incorporated herein by reference: polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

Use of a long-term sustained release implant may be particularly suitable for treatment of established neurological or psychiatric diseases or disorders as well as subjects at risk of developing a neurological or psychiatric disease or disorder. "Long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 7 days, and preferably at least 30-60 days or more. The implant may be positioned at or near the site of the cell damage, for example at or near a damaged region of the brain etc. The implant may also be placed at or near other tissues or regions affected by or involved in the neurological or psychiatric disease or disorder. Long-term sustained release implants are well known to those of ordinary skill in the art and include some of the release systems described above.

Some embodiments of the invention include methods for treating a subject to reduce the risk of a disorder associated with a neurological or psychiatric disease or disorder. The methods involve selecting and administering to a subject who is known to have, is suspected of having, or is at risk of having a neurological or psychiatric disease or disorder, an pharmaceutical agent or therapy for preventing or treating the disorder.

Another aspect of the invention involves reducing the risk of a neurological or psychiatric disease or disorder, by the use of one or more therapies and/or medications to alter functional connectivity thereby reducing, for example, the subject's risk of a neurological or psychiatric disease or disorder.

In a subject determined to have a neurological or psychiatric disease or disorder, an effective amount of an agent or therapy for preventing or treating the disease or disorder is that amount effective to alter functional connectivity of two or more neural network nodes in a subject. For example, in the case of AD, increasing functional connectivity of two or more neural network nodes selected from the group of the left dorsolateral prefrontal (DLPFC), posterior parietal (PPC), and medial frontal (MFC) cortices, may be useful as a treatment for AD in a subject.

A pharmaceutical agent and/or therapy for prevention and/or treatment of a neurological or psychiatric disease or disorder may also be selected by determining the functional connectivity of two or more neural network nodes of a subject and selecting a pharmaceutical agent that is predicted to effectively alter the functional connectivity of the two or more neural network nodes in the subject. In addition to the assays of the invention, other assays known can be used in conjunction with the methods of the invention to select a pharmaceutical agent or therapeutic regimen for the treatment of a neurological or psychiatric

disease or disorder. For example, the behavioral and neurological diagnostic methods that are used to ascertain the likelihood that a subject has a neurological or psychiatric disease or disorder, and to determine the putative stage of the disease can be used in conjunction with the methods of the invention to ascertain the level of response to a prophylactic and/or treatment of the subject. The therapeutic regimen, e.g. the amount or timing of the administration of a pharmaceutical agent and/or therapy may be varied for example by increasing or decreasing the amount of a therapeutic composition, by changing the therapeutic composition administered, by changing the route of administration, by changing the dosage timing and so on. The effective amount will vary with the particular condition being treated, the age and physical condition of the subject being treated, the severity of the condition, the duration of the treatment, the nature of the concurrent therapy (if any), the specific route of administration, and other factors within the knowledge and expertise of the health practitioner.

The factors involved in determining an effective amount are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is generally preferred that a maximum dose of the pharmacological agents and/or therapies of the invention (alone or in combination with other therapeutic agents and/or therapies) be used, that is, the highest safe dose according to sound medical judgment. It will be understood by those of ordinary skill in the art however, that a patient may insist upon a lower dose or tolerable dose or therapeutic regimen for medical reasons, psychological reasons or for virtually any other reasons.

The therapeutically effective amount of a pharmacological agent or therapy of the invention is that amount effective to alter functional connectivity of two or more neural network nodes and reduce, prevent, ameliorate, or eliminate a neurological or psychiatric disease or disorder. Additional tests useful for monitoring the onset, progression, and/or remission, of neurological or psychiatric diseases or disorders such as those described above herein, are well known to those of ordinary skill in the art. As would be understood by one of ordinary skill, for some disorders (e.g. AD, Parkinson's disease, etc.) an effective amount would be the amount of a pharmacological agent and/or therapy identified using an assay of the invention that increases and/or decreases the functional connectivity of one or more sets of two or more neural network nodes levels to a level of functional connectivity that diminishes the disorder, as determined by the aforementioned tests. Thus, the methods of the invention can be used to select a method of treating a neurological or psychiatric disease or

disorder and/or to determine effective amounts of therapeutic compounds, therapies, or other treatments for subjects with a neurological or psychiatric disease or disorder.

In the case of treating a particular disease or disorder the desired response is inhibiting the progression of the disease or condition. This may involve only slowing the progression of the disease temporarily, although more preferably, it involves halting the progression of the disease permanently. This can be monitored by the methods of the invention and/or by routine diagnostic methods known to one of ordinary skill in the art for any particular disease. The desired response to treatment of the disease or condition also can be delaying the onset or even preventing the onset of the disease or condition.

The pharmaceutical compositions used in the foregoing methods preferably are sterile and contain an effective amount of a pharmacological agent for producing the desired response in a unit of weight or volume suitable for administration to a patient.

The doses of pharmacological agents administered to a subject can be chosen in accordance with different parameters, in particular in accordance with the mode of administration used and the state of the subject. Other factors include the desired period of treatment. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. The dosage of a pharmacological agent of the invention may be adjusted by the individual physician or veterinarian, particularly in the event of any complication. A therapeutically effective amount typically varies from 0.01 mg/kg to about 1000 mg/kg, preferably from about 0.1 mg/kg to about 200 mg/kg, and most preferably from about 0.2 mg/kg to about 20 mg/kg, in one or more dose administrations daily, for one or more days.

Administration of pharmacological agents and/or therapies of the invention to mammals other than humans, e.g. for testing purposes or veterinary therapeutic purposes, is carried out under substantially the same conditions as described above. It will be understood by one of ordinary skill in the art that this invention is applicable to both human and animal diseases and disorders including neurological or psychiatric disorders or diseases. Thus, this invention is intended for use in husbandry and veterinary medicine as well as in human therapeutics.

The invention will be more fully understood by reference to the following examples. These examples, however, are merely intended to illustrate the embodiments of the invention and are not to be construed to limit the scope of the invention

Examples

Example 1

Assessment of Connectivity of Neural Network Nodes during a Working Memory Task

Introduction

Functional MRI (fMRI) has been utilized to determine whether fMRI can predict response to treatment in Alzheimer's Disease (AD) using functional connectivity of working memory network nodes.

In an N-back task, a subject is shown a string of letters, one letter at a time. The subject must recall whether a currently presented letter matches the Nth preceding letter. The N-back test has been used extensively to stimulate areas of the brain during acquisition of functional MRI images. In particular, the N-back test is known to stimulate bilateral dorsolateral prefrontal, dorsolateral parietal, and medial frontal cortical activity. Such tests are discussed in Braver, T.S., et al. *Neuroimage* 1997, 5:49-62. Although these tests may show which regions of a subject's brain were used at some time during the N-back task, they do not show when those regions were used, for how long those regions were used, and which regions were being used at the same time.

We have utilized fMRI in conjunction with an N-back task to assess the connectivity of two or more neural network regions. We utilized the determination of functional connectivity to illustrate the presence of a synchronous relationship between one node and another. We used time-segment analysis of functional connectivity to determine increasing or decreasing synchrony, which indicated recruitment of brain regions or refinement or functional connectivity with a sustained behavior.

Methods

Twelve AD patients (5 male and 7 female) and three controls performed a simplified 1-back working memory/executive function task during whole brain blood oxygenation level-dependent (BOLD) fMRI (1.5T, gradient recall echo (GRE), relaxation time/echo time (TR/TE) =3000/60, flip angle (FA) =90, 64x64 matrix, field of view (FOV) =24, slice thickness=5mm, no skip, 240 TRs) and a right hand-flexion task. All the patient s had memory impairment on dementia rating scale (DRS), nine had initiation/perseveration scale scores below cut-off, three had construction problems, two had conceptualization problems, and one had a language impairment.

The "easy" 1-back: a letter was presented visually to the subject in scanner every three seconds and the subject was to respond with button-press "yes" if letter matched same letter as letter that was seen immediately before or to button-press "no" if not. (2.5sec standard deviation (SD), -.5sec ISI). The baseline task was "letter H" vigilance. This involved showing a letter every three seconds and having the subject press "yes" button if the letter was H, or the "no" button if the letter was not H. The testing alternated between the letter H and 1-back for eight cycles, with each cycle lasting 75 seconds.

The twelve patients were treated with galantamine up to 8mg twice a day. At the end of eight weeks, caregivers filled out a Social Behavior Scale (Boada-Rovera, *Drugs & Aging* 2004;21(1):43-53) as the primary efficacy measure to determine responders and non-responders. The fMRI analyses were conducted blinded to treatment response. Region of interest (ROI) kernels of 340mm^3 in LDLPFC, LMFC, LPPC, and LOTC were chosen from Talaraiched coordinates in 1- back maps of normal subjects (3 in-network, one out-of-network). Whole-brain voxel-wise cross correlations were conducted using ideal waveforms derived from mean BOLD signal in these ROI kernels. Averaged waveforms for each ROI for each subject were generated and used for connectivity correlations for 1back. All 1-back ROI's were re-used for hand flexion task.

The 340mm^3 regions of interest (ROIs) (referred to herein as kernels) were generated within empirically defined, task-specific regions of the left dorsolateral prefrontal (DLPFC), posterior parietal (PPC), and medial frontal (MFC) cortices. An area in the left occipitotemporal cortex (OT) was chosen as a control ROI. For each ROI, mean BOLD signal time courses were compared to each voxel in the entire brain using a voxel-wise cross-correlation procedure (Biswal B. et al., *Magnetic Resonance Med.* 1995, 34:537-541). Mean ROI correlation coefficients ranks were calculated for each subject to test correlation strength in the control, responder, and nonresponder groups.

Results

Performance on the 1-back was comparable for all AD patients and controls. (Fig. 4). All patients performed as well as controls on computerized 1back. There were no learning effects over time. Both Responders and Non-responders (based on SBS) performed equally well on a clock-drawing task and 1-back pre- and post-treatment and did not change over time. The clock-drawing task and the social behavior scale are neuropsychological tests performed by each subject in addition to the care-giver observations.

Four of the twelve AD patients were responders to galantamine, according to caregiver Social Behavior Scale ratings. The fMRI functional connectivity maps revealed that controls and responders had strongly correlated co-activations in all nodes of the 1-back network (DLPFC,PPC,MFC), when the left MFC ROI is chosen for correlation (Figs. 5, 6). When the left MFC ROI was chosen for correlation in the eight AD non-responders, all eight had co-activation of adjacent MFC and five had co-activation in bilateral DLPFC, but none co-activated the PPC. The control OT ROI brought out the 1-back network in only one AD non-responder, but not in other AD or control subjects. The DLPFC, PPC, and OT ROI results are shown in Fig. 6. Mean correlation coefficients for each ROI were ranked and Wilcoxon signed rank tests revealed that MFC/PPC ranks were significantly lower for AD non-responders compared to responders and age-matched controls. Functional connectivity analysis of 1-back ROIs using the hand-flex data revealed no co-activations.

There is increasing evidence that improved frontal lobe function underlies the treatment effects of AD medications (Boada-Rovera, *Drugs & Aging* 2004;21(1):43-53; Biswal, B. et al., *Magnetic Resonance Med.* 1995; 34:537-541). In AD patients who will respond to galantamine, the 1-back network of MFC, DLPFC, and PPC is functionally connected, as in controls. This suggests that frontal lobe behavioral improvement in treatment responders requires the synchrony of the executive network with MFC. The functional desynchronization between frontal and parietal ROIs in AD patients who will not respond to galantamine suggests that their ability to perform the 1-back reflects a compensatory reserve capacity. This pre-treatment disrupted connectivity in AD non-responders prevents frontal behavior improvement with galantamine. The results indicate that functional connectivity mapping of neural network nodes with fMRI provides a useful biomarker to predict treatment response in AD and other neuropsychiatric illnesses.

Example 2

Assessment of Connectivity of Neural Network Nodes during a Motor Task

Methods

A set of AD patients and controls perform a simple motor function task. For the task, subjects are instructed to repetitively open and close their right hand at a self-paced, consistent rate over a 45-sec period. The opening/closing activity is alternated with a 45-sec rest phase in a four-cycle blocked-paradigm over a six-minute period (i.e., 120 repetitions of the 3-sec TR GRE-EPI acquisition). Subjects repeat two runs of this task and the data is

concatenated to produce one contiguous dataset for analysis. The testing is performed during whole brain blood oxygenation level-dependent (BOLD) fMRI (1.5T, GRE, TR/TE=3000/60, FA=90, 64x64 matrix, FOV=24, slice thickness=5mm, no skip, 120 TRs).

Some subjects are treated with a pharmaceutical agent (for example: administration of galantamine to a subject as a treatment for AD). At the end of a drug administration period, caregivers fill out a Social Behavior Scale (Boada-Rovera, *Drugs & Aging* 2004;21(1):43-53) as the primary efficacy measure to determine responders and non-responders. The fMRI analyses are conducted blinded to treatment response. 340mm^3 regions of interest (ROIs) are generated within empirically defined, task-specific regions of the left dorsolateral prefrontal (DLPFC), posterior parietal (PPC), and medial frontal (MFC) cortices. An area in the left occipitotemporal cortex (OT) is chosen as a control ROI. For each ROI, mean BOLD signal time courses are compared to each voxel in the entire brain using a voxel-wise cross-correlation procedure (Biswal, B. et al., *Magnetic Resonance Med.* 1995: 34:537-541). Mean ROI correlation coefficients ranks are calculated for each subject to test correlation strength in the control, responder, and non-responder groups.

Results

The performance on the motor function task is compared for all the AD patients and controls. Caregiver Social Behavior Scale ratings are also assessed. The fMRI functional connectivity maps provide information on the connectivity of two or more neural network nodes in subjects and the connectivity is compared to control connectivity of the two or more neural network nodes as a biomarker for psychiatric or neurological disease or disorders and as a predictor or indication of whether or not the subject will respond to a pharmaceutical agent for the treatment of the psychiatric or neurological disease or disorder. The results indicate that functional connectivity mapping with fMRI may provide a biomarker to predict treatment response in AD and other neurological or psychiatric disease or disorder.

Example 3

Assessment of Connectivity of Neural Network Nodes during a Visuospatial Processing Task

A set of AD patients and controls perform a visuospatial processing task. Data acquisition and data processing methods used in this example are the same as those used in Example 1. However, in this example, the task that the subjects are asked to perform is intended to stimulate neural activity associated with visuospatial processing. The visuospatial

task performed by the subjects is an adaptation of a widely used pencil-and-paper test of non-verbal intelligence: Wechsler Adult Intelligence Scale (WAIS-III). This task can be understood with reference to Fig. 7, which shows an exemplary sequence of slides used in this task

During the reference intervals, a control task is performed. In it, a series of slides showing symbol groupings is presented to the subject. Two symbol groups are arranged on each slide: the upper group is a row of two symbols; the lower group, beneath the upper group, is a row of five symbols. One symbol in either grouping is missing. On a two-button keypad, the subject presses the button corresponding to the side of the slide that has the missing symbol.

During the task intervals, a symbol-search task is performed. In it, a series of symbol groupings, arranged in the same manner as in the control task, is presented. However, in this case, either symbol from the top grouping is a target for a possible match in the bottom grouping. The subject is instructed to indicate whether one of the target symbols from the top grouping is located in the bottom grouping. A left button press indicates a positive match and a right button press indicates no match. Both the control task and the symbol-search tasks are self-paced by the subject over a period of 45 seconds. The tasks are alternately performed during 45-second intervals during four task intervals over a six-minute period (i.e., 120 repetitions of the 3-second TR GRE-EPI acquisition). Subjects repeat two runs of this task and the resulting data is concatenated to produce one contiguous dataset for analysis.

The adaptation of the WAIS-III test used in this experiment differs slightly from the standard test. In the standard test, the target symbols are located horizontally from the choice symbol group; whereas in the modified version used in the present experiment, the symbol groups are vertically offset from one another. This modification is not expected to have a significant effect on subject performance, as the geometry of the symbols is, in general, of sufficient complexity to enforce a memory component to the task.

A sequence of magnetic resonance images are obtained while the test subject performs the visuospatial processing task. fMRI images are collected and show connectivity of two or more neural network nodes in regions consistent with the visual, working memory and decision-making requirements of the task.

Some subjects are treated with a pharmaceutical agent (for example: administration of galantamine to a subject as a treatment for AD). At the end of a drug administration period, caregivers fill out a Social Behavior Scale (Boada-Rovera, *Drugs & Aging* 2004;21(1):43-53)

as the primary efficacy measure to determine responders and non-responders. The fMRI analyses are conducted blinded to treatment response. 340mm^3 regions of interest (ROIs) are generated within empirically defined, task-specific regions of the left dorsolateral prefrontal (DLPFC), posterior parietal (PPC), and medial frontal (MFC) cortices. An area in the left occipitotemporal cortex (OT) is chosen as a control ROI. For each ROI, mean BOLD signal time courses are compared to each voxel in the entire brain using a voxel-wise cross-correlation procedure (Biswal, B., et al., *Magnetic Resonance Med.* 1005; 34:5367-541). Mean ROI correlation coefficients ranks are calculated for each subject to test correlation strength in the control, responder, and non-responder groups.

The performance on the visuospatial processing task is compared for all the AD patients and controls. Caregiver Social Behavior Scale ratings may also be assessed. The fMRI functional connectivity maps provide information on connectivity of two or more neural network nodes in the subjects and the results from the subject are compared to control connectivity of two or more neural network nodes as a biomarker for psychiatric or neurological disease or disorders and as a predictor or indication of whether or not the subject will respond to a pharmaceutical agent for the treatment of the psychiatric or neurological disease or disorder.

Example 4

Assessment of Connectivity of Neural Network Nodes during Rest (non-task)

Functional MRI assessment of a set of AD patients and controls is done while the subjects are at rest, e.g. while subjects are not perform a task. The assessment is performed during whole brain blood oxygenation level-dependent (BOLD) fMRI (1.5T, GRE, TR/TE=3000/60, FA=90, 64x64 matrix, FOV=24, slice thickness=5mm, no skip, 120 TRs). Some subjects may be treated with a pharmaceutical agent (for example: administration of galantamine to a subject as a treatment for AD). At the end of a drug administration period, caregivers fill out a Social Behavior Scale (Boada-Rovera, *Drugs & Aging* 2004;21(1):43-53) as the primary efficacy measure to determine responders and non-responders. The fMRI analyses are conducted blinded to treatment response. 340mm^3 regions of interest (ROIs) are generated within empirically defined, task-specific regions of the left dorsolateral prefrontal (DLPFC), posterior parietal (PPC), and medial frontal (MFC) cortices. An area in the left occipitotemporal cortex (OT) is chosen as a control ROI. For each ROI, mean BOLD signal time courses are compared to each voxel in the entire brain using a voxel-wise cross-

correlation procedure (Biswal, B., et al., *Magnetic Resonance Med.* 1005; 34:537-541). Mean ROI correlation coefficients ranks are calculated for each subject to test correlation strength in the control, responder, and non-responder groups.

Results

The fMRI results from resting (non-task performing) subjects are compared for all the AD patients and controls. Caregiver Social Behavior Scale ratings are also assessed. The fMRI functional connectivity maps provide information on the connectivity of two or more neural network nodes in the subject and the connectivity of the nodes may be compared to control neural network activation as a biomarker for psychiatric or neurological disease or disorders and/or as a predictor or indication of whether or not the subject will respond to a pharmaceutical agent for the treatment of the psychiatric or neurological disease or disorder. The results indicate that functional connectivity mapping with fMRI may provide a biomarker to predict treatment response in AD and other neurological and/or psychiatric illnesses.

Example 5

Non-Stationary Noise

As noted above, there is always a certain amount of background neural activity in the brain. When the neural network node activity is observed as in the foregoing examples, neural activity is observed that differs from this background in a statistically significant manner. In the terminology of stochastic processes, this background represents stationary noise. Thus, as in the foregoing examples, we observe the neural network node activity against a backdrop of stationary noise.

It is also possible to observe the neural network node activity against a background of non-stationary noise. For example, the neural activity in one region of the subject's brain is viewed against the background of neural activity in another region of the subject's brain. Data derived from such observations indicates whether or not those two regions of the subject's brain are functionally linked.

Data acquisition and data processing methods used in this example were the same as those used in Example 1. The test subjects performed the same working-memory task discussed in Example 1, 2, 3, or 4 or were recorded at rest – e.g. not while doing a task. Time-segment analysis and correlation methods such as that disclosed in this example are useful in demonstrating dynamic changes in other functionally related neural networks with

different fMRI tasks and for the removal of background noise in the assessment of the connectivity of two or more neural network nodes in a subject. In some experiments, the subject is undertaking a task and in other experiments the subject is tested while resting - e.g. while not engaged in a task.

Summary

In these experiments, we demonstrate a new method for determining the functional connectivity of two or more neural network nodes in a subject during a task and/or at rest. The results of these experiments indicate that functional connectivity of two or more neural network nodes can be used as a biomarker for the prediction or indication of whether or not a pharmaceutical agent will be effective in the treatment of a neurological or psychiatric disease or disorder in a subject. The experiments also allow determination of a treatment effect of a pharmaceutical agent on a subject's neurological or psychiatric disease or disorder, for example by testing after (or before and after) administration of a pharmaceutical agent to determine a change in connectivity of regions in the subject's brain. Such experiments are also useful to screen for effective pharmaceutical agents for treatment for neurological and/or psychiatric diseases or disorders.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

All references disclosed herein, including patent documents, are incorporated by reference in their entirety.

The terms and expressions that have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, it being recognized that various modifications are possible within the scope of the invention.

Except where explicitly described otherwise, terms used in the singular also are meant to embrace the plural, and vice versa.

I claim:

Claims

1. A method for assessing the likelihood of a subject to have a therapeutic response to a pharmaceutical agent or therapy, comprising

determining a functional connectivity of two or more neural network nodes in a subject performing a task, wherein the subject is known to have or suspected of having a neurological or psychiatric disease or disorder;

comparing the functional connectivity of the two or more neural network nodes in the subject to a control functional connectivity of the two or more neural network nodes, and

assessing the likelihood that the subject will have a therapeutic response to a pharmaceutical agent or therapy based on the comparison of the test and control functional connectivity of the two or more neural network nodes.

2. The method of claim 1, wherein the control functional connectivity is a functional connectivity previously determined in the subject performing the task.

3. The method of claim 1, wherein the control functional connectivity is the functional connectivity in a control subject performing the task.

4. The method of claim 3, wherein the control subject does not have the neurological or psychiatric disease or disorder.

5. The method of claim 3, wherein the control subject has the neurological or psychiatric disease or disorder.

6. The method of claim 1, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, dementia unspecified, multiple sclerosis, depression, anxiety, obsessive compulsive disorder, brain injury, schizophrenia, a sensory neuropathy, a motor neuropathy, a psychotic disorder, migraine, epilepsy, tremor, an affective disorder, stroke, or stroke recovery.

7. The method of claim 6, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease.

8. The method of claim 1, wherein the two or more neural network nodes are located in the left dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), and/or medial frontal cortex (MFC).

9. The method of claim 1, wherein the neural network node is a control neural network node.

10. The method of claim 9, wherein the control neural network node is in the occipitotemporal cortex (OT).

11. The method of claim 1, wherein the task comprises an N-back task.

12. The method of claim 1, wherein the task comprises a cognitive task.

13. The method of claim 12, wherein the cognitive task comprises a semantic reasoning task or a visuospatial recognition task.

14. The method of claim 1, wherein the task comprises a motor task.

15. The method of claim 1, wherein the task comprises a sensory task.

16. The method of claim 1, wherein the task is a self-paced task or an externally paced task.

17. The method of claim 1, wherein the method of determining the functional connectivity of two or more neural network nodes in the subject comprises obtaining a sequence of functional magnetic resonance (fMRI) images of the subject during performance of the task.

18. The method of claim 1, wherein the method of determining the functional connectivity of two or more neural network nodes in the subject comprises: collecting task data indicative of functional connectivity of two or more neural network nodes during performance of the task; and filtering, from the task data, a contribution to the task data

arising from background neural activity.

19. The method of claim 18, wherein the background neural activity comprises neural activity associated with performance of a reference task.

20. The method of claim 18, wherein the background neural activity comprises neural activity associated with a selected brain region of the subject.

21. The method of claim 20, wherein the selected brain region is a region outside the neural network nodes.

22. The method of claim 18, wherein the background neural activity comprises neural activity associated with the selected region during performance of the task.

23. The method of claim 1, wherein determining the functional connectivity of two or more neural network nodes comprises:

having the subject perform the task during a first plurality of task intervals, each having at least a first time segment and a second time segment,

collecting data from each of the first time segments into a first data set,

collecting data from each of the second time segments into a second data set; and

filtering, from the first and second data sets, a contribution to the first and second data sets arising from background neural activity.

24. The method of claim 23, wherein filtering comprises performing a correlation between data representative of the background neural activity and the first and second data sets.

25. The method of claim 23, wherein filtering comprises performing a statistical test between data representative of the background neural activity and the first and second data sets.

26. The method of claim 1, wherein the pharmaceutical agent or therapy is for the treatment of the neurological or psychiatric disease or disorder.

27. The method of claim 26, wherein the pharmaceutical agent is a selective serotonin reuptake inhibitor (SSRI)/antidepressant, a psychostimulant, an N-methyl-D-asparate (NMDA) receptor modulator, an antipsychotic, an anxiolytic, a dopamine/dopaminergic agent, an immune-modulating agent, a cholinesterase inhibitor, or a GABAergic agent.

28. The method of claim 27,wherein the cholinesterase inhibitor is galantamine.

29. The method of claim 26, wherein the therapy comprises application of a medical device or brain surgery.

30. The method of claim 29, wherein the medical device is deep brain stimulation, vagus nerve stimulation, or transcranial magnetic stimulation.

31. A method for selecting a therapeutic regimen for a subject known to have or suspected of having a neurological or psychiatric disease or disorder comprising:

determining a functional connectivity of two or more neural network nodes in a subject performing a task, comparing the functional connectivity of the two or more neural network nodes in the subject to a control functional connectivity of the two or more neural network nodes, and

selecting a therapeutic regimen for the subject based on the comparison of the test and control functional connectivity of the two or more neural network nodes.

32. The method of claim 31, wherein the control functional connectivity is a functional connectivity previously determined in the subject performing the task.

33. The method of claim 31, wherein the control functional connectivity is the functional connectivity in a control subject performing the task.

34. The method of claim 33, wherein the control subject does not have the neurological or psychiatric disease or disorder.

35. The method of claim 33, wherein the control subject has the neurological or

psychiatric disease or disorder.

36. The method of claim 31, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, dementia unspecified, multiple sclerosis, depression, anxiety, obsessive compulsive disorder, brain injury, schizophrenia, a sensory neuropathy, a motor neuropathy, a psychotic disorder, migraine, epilepsy, tremor, an affective disorder, stroke, or stroke recovery.

37. The method of claim 36, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease.

38. The method of claim 31, wherein the two or more neural network nodes are located in the left dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), and/or medial frontal cortex (MFC).

39. The method of claim 31, wherein a neural network node is a control neural network node.

40. The method of claim 39, wherein the control neural network node is in the occipitotemporal cortex (OT).

41. The method of claim 31, wherein the task comprises an N-back task.

42. The method of claim 31, wherein the task comprises a cognitive task.

43. The method of claim 38, wherein the cognitive task comprises a semantic reasoning task or a visuospatial recognition task.

44. The method of claim 31, wherein the task comprises a motor task.

45. The method of claim 31, wherein the task comprises a sensory task.

46. The method of claim 31, wherein the task is a self-paced task or an externally paced task.

47. The method of claim 31, wherein the method of determining the functional connectivity of two or more neural network nodes in the subject comprises obtaining a sequence of functional magnetic resonance (fMRI) images of the test subject during performance of the task.

48. The method of claim 31, wherein the method of determining the functional connectivity of two or more neural network nodes in the subject comprises: collecting task data indicative of functional connectivity of two or more neural network nodes during performance of the task; and filtering, from the task data, a contribution to the task data arising from background neural activity.

49. The method of claim 48, wherein the background neural activity comprises neural activity associated with performance of a reference task.

50. The method of claim 48, wherein the background neural activity comprises neural activity associated with a selected brain region of the subject.

51. The method of claim 50, wherein the selected brain region is a region outside the neural network nodes.

52. The method of claim 48, wherein the background neural activity comprises neural activity associated with the selected region during performance of the task.

53. The method of claim 31, wherein determining the functional connectivity of two or more neural network nodes comprises:

having the subject perform the task during a first plurality of task intervals, each having at least a first time segment and a second time segment,

collecting data from each of the first time segments into a first data set,

collecting data from each of the second time segments into a second data set; and

filtering, from the first and second data sets, a contribution to the first and second data

sets arising from background neural activity.

54. The method of claim 53, wherein filtering comprises performing a correlation between data representative of the background neural activity and the first and second data sets.

55. The method of claim 53, wherein filtering comprises performing a statistical test between data representative of the background neural activity and the first and second data sets.

56. The method of claim 31, wherein the therapeutic regimen comprises administering a pharmaceutical agent or therapy.

57. The method of claim 56, wherein the pharmaceutical agent is a selective serotonin reuptake inhibitor (SSRI)/antidepressant, a psychostimulant, an N-methyl-D-asparate (NMDA) receptor modulator, an antipsychotic, an anxiolytic, a dopamine/dopaminergic agent, an immune-modulating agent, a cholinesterase inhibitor, or a GABAergic agent.

58. The method of claim 57,wherein the cholinesterase inhibitor is galantamine.

59. The method of claim 56, wherein the therapy comprises application of a medical device or brain surgery.

60. The method of claim 59, wherein the medical device is deep brain stimulation, vagus nerve stimulation, or transcranial magnetic stimulation.

61. A method for identifying the onset, progression, or regression of a neurological or psychiatric disease or disorder in a subject, comprising

determining a first functional connectivity of two or more neural network nodes in a subject performing a task,

determining a second functional connectivity of two or more neural network nodes in the subject performing the task at a time later than the determination of the first functional connectivity of the two or more neural network nodes in the subject performing the task, and

comparing the first functional connectivity of the two or more neural network nodes to the second functional connectivity of the two or more neural network nodes, wherein a difference between the first and second functional connectivity of the two or more neural network nodes identifies the onset, progression, or regression of the neurological or psychiatric disease or disorder in the subject.

62. The method of claim 61, wherein an increase or decrease in the second functional connectivity of the two or more neural network nodes compared to the first functional connectivity of the two or more neural network nodes indicates the onset or progression of the neurological or psychiatric disease or disorder in the subject.

63. The method of claim 61, wherein an increase or decrease in the second functional connectivity of the two or more neural network nodes compared to the first functional connectivity of the two or more neural network nodes indicates the regression of the neurological or psychiatric disease or disorder in the subject.

64. The method of claim 61, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, dementia unspecified, multiple sclerosis, depression, anxiety, obsessive compulsive disorder, brain injury, schizophrenia, a sensory neuropathy, a motor neuropathy, a psychotic disorder, migraine, epilepsy, tremor, an affective disorder, stroke, or stroke recovery.

65. The method of claim 64, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease.

66. The method of claim 61, wherein the two or more neural network nodes are located in the left dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), and/or medial frontal cortex (MFC).

67. The method of claim 61, wherein a neural network node is a control neural network node.

68. The method of claim 67, wherein the control neural network node is in the

occipitotemporal cortex (OT).

69. The method of claim 61, wherein the task comprises an N-back task.

70. The method of claim 61, wherein the task comprises a cognitive task.

71. The method of claim 70, wherein the cognitive task comprises a semantic reasoning task or a visuospatial recognition task.

72. The method of claim 61, wherein the task comprises a motor task.

73. The method of claim 61, wherein the task comprises a sensory task.

74. The method of claim 61, wherein the task is a self-paced task or an externally paced task.

75. The method of claim 61, wherein the method of determining the functional connectivity of two or more neural network nodes in the subject comprises obtaining a sequence of functional magnetic resonance (fMRI) images of the subject during performance of the task.

76. The method of claim 61, wherein the method of determining the functional connectivity of two or more neural network nodes in the subject comprises: collecting task data indicative of functional connectivity of two or more neural network nodes during performance of the task; and filtering, from the task data, a contribution to the task data arising from background neural activity.

77. The method of claim 76, wherein the background neural activity comprises neural activity associated with performance of a reference task.

78. The method of claim 76, wherein the background neural activity comprises neural activity associated with a selected brain region of the subject.

79. The method of claim 78, wherein the selected brain region is a region outside the neural network nodes.

80. The method of claim 76, wherein the background neural activity comprises neural activity associated with the selected region during performance of the task.

81. The method of claim 61, wherein determining the functional connectivity of two or more neural network nodes comprises:

having the subject perform the task during a first plurality of task intervals, each having at least a first time segment and a second time segment,

collecting data from each of the first time segments into a first data set,

collecting data from each of the second time segments into a second data set; and

filtering, from the first and second data sets, a contribution to the first and second data sets arising from background neural activity.

82. The method of claim 81, wherein filtering comprises performing a correlation between data representative of the background neural activity and the first and second data sets.

83. The method of claim 81, wherein filtering comprises performing a statistical test between data representative of the background neural activity and the first and second data sets.

84. The method of claim 61, wherein the subject has been administered a pharmaceutical agent or therapy as a treatment for the neurological or psychiatric disease or disorder.

85. The method of claim 84, wherein the pharmaceutical agent or therapy is administered between the time of the first and second determinations of the functional connectivity of the two or more neural network nodes in the subject.

86. The method of claim 84, wherein the pharmaceutical agent is a selective serotonin reuptake inhibitor (SSRI)/antidepressant, a psychostimulant, an N-methyl-D-asparate (NMDA) receptor modulator, an antipsychotic, an anxiolytic, a dopamine/dopaminergic

agent, an immune-modulating agent, a cholinesterase inhibitor, or a GABAergic agent.

87. The method of claim 86,wherein the cholinesterase inhibitor is galantamine.

88. The method of claim 84, wherein the therapy comprises application of a medical device or brain surgery.

89. The method of claim 88, wherein the medical device is deep brain stimulation, vagus nerve stimulation, or transcranial magnetic stimulation.

90. A method for identifying a candidate pharmaceutical agent or therapy for preventing or treating a neurological or psychiatric disorder, comprising

determining a first functional connectivity of two or more neural network nodes in a subject performing a task, wherein the subject has a neurological or psychiatric disease or disorder,

administering a candidate pharmaceutical agent or therapy to the subject,

determining after the administration of the candidate pharmaceutical agent or therapy a second functional connectivity of the two or more neural network nodes in the subject performing the task, and

comparing the first and second functional connectivity of the two or more neural network nodes in the subject, wherein a difference between the first and second functional connectivity of the two or more neural networks nodes in the subject identifies the candidate pharmaceutical agent or therapy for preventing or treating the neurological or psychiatric disease or disorder.

91. The method of claim 90, wherein the difference is an increase in the second functional connectivity of the two or more neural network nodes in the subject compared to the first functional connectivity of the two or more neural network nodes.

92. The method of claim 90, wherein the control functional connectivity is a functional connectivity previously determined in the subject performing the task.

93. The method of claim 90, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, dementia

unspecified, multiple sclerosis, depression, anxiety, obsessive compulsive disorder, brain injury, schizophrenia, a sensory neuropathy, a motor neuropathy, a psychotic disorder, migraine, epilepsy, tremor, an affective disorder, stroke, or stroke recovery.

94. The method of claim 93, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease.

95. The method of claim 90, wherein the two or more neural network nodes are located in the left dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), and/or medial frontal cortex (MFC).

96. The method of claim 90, wherein a neural network node is a control neural network node.

97. The method of claim 96, wherein the control neural network node is in the occipitotemporal cortex (OT).

98. The method of claim 90, wherein the task comprises an N-back task.

99. The method of claim 90, wherein the task comprises a cognitive task.

100. The method of claim 99, wherein the cognitive task comprises a semantic reasoning task or a visuospatial recognition task.

101. The method of claim 90, wherein the task comprises a motor task.

102. The method of claim 90, wherein the task comprises a sensory task.

103. The method of claim 90, wherein the task is a self-paced task or an externally paced task.

104. The method of claim 90, wherein the method of determining the functional connectivity of two or more neural network nodes in the subject comprises obtaining a

sequence of functional magnetic resonance (fMRI) images of the subject during performance of the task.

105. The method of claim 90, wherein the method of determining the functional connectivity of two or more neural network nodes in the subject comprises: collecting task data indicative of functional connectivity of two or more neural network nodes during performance of the task; and filtering, from the task data, a contribution to the task data arising from background neural activity.

106. The method of claim 105, wherein the background neural activity comprises neural activity associated with performance of a reference task.

107. The method of claim 105, wherein the background neural activity comprises neural activity associated with a selected brain region of the subject.

108. The method of claim 107, wherein the selected brain region is a region outside the neural network nodes.

109. The method of claim 105, wherein the background neural activity comprises neural activity associated with the selected region during performance of the task.

110. The method of claim 90, wherein determining the functional connectivity of two or more neural network nodes comprises:

having the subject perform the task during a first plurality of task intervals, each having at least a first time segment and a second time segment,

collecting data from each of the first time segments into a first data set,

collecting data from each of the second time segments into a second data set; and

filtering, from the first and second data sets, a contribution to the first and second data sets arising from background neural activity.

111. The method of claim 110, wherein filtering comprises performing a correlation between data representative of the background neural activity and the first and second data sets.

112. The method of claim 110, wherein filtering comprises performing a statistical test between data representative of the background neural activity and the first and second data sets.

113. The method of claim 90, wherein the candidate pharmaceutical agent is a selective serotonin reuptake inhibitor (SSRI)/antidepressant, a psychostimulant, an N-methyl-D-asparate (NMDA) receptor modulator, an antipsychotic, an anxiolytic, a dopamine/dopaminergic agent, an immune-modulating agent, a cholinesterase inhibitor, or a GABAergic agent.

114. The method of claim 90, wherein the therapy is use of a medical device or brain surgery.

115. A method for assessing the likelihood of a subject to have a therapeutic response to a pharmaceutical agent or therapy, comprising

determining a resting functional connectivity of two or more neural network nodes in a subject, wherein the subject is known to have or suspected of having a neurological or psychiatric disease or disorder;

comparing the resting functional connectivity of the two or more neural network nodes in the subject to a control resting functional connectivity of the two or more neural network nodes, and

assessing the likelihood that the subject will have a therapeutic response to a pharmaceutical agent or therapy based on the comparison of the test and control resting functional connectivity of the two or more neural network nodes.

116. The method of claim 115, wherein the control resting functional connectivity is a resting functional connectivity previously determined in the subject.

117. The method of claim 115, wherein the control resting functional connectivity is the resting functional connectivity in a control subject.

118. The method of claim 117, wherein the control subject does not have the neurological

or psychiatric disease or disorder.

119. The method of claim 117, wherein the control subject has the neurological or psychiatric disease or disorder.

120. The method of claim 115, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, dementia unspecified, multiple sclerosis, depression, anxiety, obsessive compulsive disorder, brain injury, schizophrenia, a sensory neuropathy, a motor neuropathy, a psychotic disorder, migraine, epilepsy, tremor, coma, an affective disorder, stroke, or stroke recovery.

121. The method of claim 120, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease.

122. The method of claim 115, wherein the two or more neural network nodes are located in the left dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), and/or medial frontal cortex (MFC).

123. The method of claim 115, wherein a neural network node is a control neural network node.

124. The method of claim 123, wherein the control neural network node is in the occipitotemporal cortex (OT).

125. The method of claim 115, wherein the method of determining the resting functional connectivity of two or more neural network nodes in the subject comprises obtaining a resting sequence of functional magnetic resonance (fMRI) images of the subject.

126. The method of claim 115, wherein the method of determining the resting functional connectivity of two or more neural network nodes in the subject comprises: collecting data indicative of resting functional connectivity of two or more neural network nodes; and filtering, from the data, a contribution to the data arising from background neural activity.

127. The method of claim 126, wherein the background neural activity comprises neural activity associated with a selected brain region of the subject.

128. The method of claim 127, wherein the selected brain region is a region outside the neural network nodes.

129. The method of claim 115, wherein determining the resting functional connectivity of two or more neural network nodes comprises:

collecting data from the subject during each of a first plurality of intervals, each having at least a first time segment and a second time segment, wherein data is collected from each of the first time segments into a first data set, and data is collected from each of the second time segments into a second data set, and

filtering, from the first and second data sets, a contribution to the first and second data sets arising from background neural activity.

130. The method of claim 129, wherein filtering comprises performing a correlation between data representative of the background neural activity and the first and second data sets.

131. The method of claim 129, wherein filtering comprises performing a statistical test between data representative of the background neural activity and the first and second data sets.

132. The method of claim 115, wherein the pharmaceutical agent or therapy is for the treatment of the neurological or psychiatric disease or disorder.

133. The method of claim 132, wherein the pharmaceutical agent is a selective serotonin reuptake inhibitor (SSRI)/antidepressant, a psychostimulant, an N-methyl-D-asparate (NMDA) receptor modulator, an antipsychotic, an anxiolytic, a dopamine/dopaminergic agent, an immune-modulating agent, a cholinesterase inhibitor, or a GABAergic agent.

134. The method of claim 133, wherein the cholinesterase inhibitor is galantamine.

135. The method of claim 132, wherein the therapy comprises application of a medical device or brain surgery.

136. The method of claim 135, wherein the medical device is deep brain stimulation, vagus nerve stimulation, or transcranial magnetic stimulation.

137. A method for selecting a therapeutic regimen for a subject known to have or suspected of having a neurological or psychiatric disease or disorder comprising:

determining a resting functional connectivity of two or more neural network nodes in a subject, comparing the resting functional connectivity of the two or more neural network nodes in the subject to a control resting functional connectivity of the two or more neural network nodes, and

selecting a therapeutic regimen for the subject based on the comparison of the test and control resting functional connectivity of the two or more neural network nodes.

138. The method of claim 137, wherein the control resting functional connectivity is a resting functional connectivity previously determined in the subject.

139. The method of claim 137, wherein the control resting functional connectivity is the resting functional connectivity in a control subject.

140. The method of claim 139, wherein the control subject does not have the neurological or psychiatric disease or disorder.

141. The method of claim 139, wherein the control subject has the neurological or psychiatric disease or disorder.

142. The method of claim 137, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, dementia unspecified, multiple sclerosis, depression, anxiety, obsessive compulsive disorder, brain injury, schizophrenia, a sensory neuropathy, a motor neuropathy, a psychotic disorder, migraine, epilepsy, tremor, coma, an affective disorder, stroke, or stroke recovery.

143. The method of claim 142, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease.

144. The method of claim 137, wherein the two or more neural network nodes are located in the left dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), and/or medial frontal cortex (MFC).

145. The method of claim 137, wherein a neural network node is a control neural network node.

146. The method of claim 145, wherein the control neural network node is in the occipitotemporal cortex (OT).

147. The method of claim 137, wherein the method of determining the resting functional connectivity of two or more neural network nodes in the subject comprises obtaining a resting sequence of functional magnetic resonance (fMRI) images of the subject.

148. The method of claim 137, wherein the method of determining the resting functional connectivity of two or more neural network nodes in the subject comprises: collecting data indicative of resting functional connectivity of two or more neural network nodes; and filtering, from the data, a contribution to the data arising from background neural activity.

149. The method of claim 148, wherein the background neural activity comprises neural activity associated with a selected brain region of the subject.

150. The method of claim 149, wherein the selected brain region is a region outside the neural network nodes.

151. The method of claim 137, wherein determining the resting functional connectivity of two or more neural network nodes comprises:

collecting data from the subject during each of a first plurality of intervals, each having at least a first time segment and a second time segment, wherein data is collected from each of the first time segments into a first data set, and data is collected from each of the

second time segments into a second data set; and

filtering, from the first and second data sets, a contribution to the first and second data sets arising from background neural activity.

152. The method of claim 151, wherein filtering comprises performing a correlation between data representative of the background neural activity and the first and second data sets.

153. The method of claim 151, wherein filtering comprises performing a statistical test between data representative of the background neural activity and the first and second data sets.

154. The method of claim 137, wherein the therapeutic regimen comprises administering a pharmaceutical agent or therapy.

155. The method of claim 154, wherein the pharmaceutical agent is a selective serotonin reuptake inhibitor (SSRI)/antidepressant, a psychostimulant, an N-methyl-D-asparate (NMDA) receptor modulator, an antipsychotic, an anxiolytic, a dopamine/dopaminergic agent, an immune-modulating agent, a cholinesterase inhibitor, or a GABAergic agent.

156. The method of claim 155, wherein the cholinesterase inhibitor is galantamine.

157. The method of claim 154, wherein the therapy comprises application of a medical device or brain surgery.

158. The method of claim 157, wherein the medical device is deep brain stimulation, vagus nerve stimulation, or transcranial magnetic stimulation.

159. A method for identifying the onset, progression, or regression of a neurological or psychiatric disease or disorder in a subject, comprising

determining a first resting functional connectivity of two or more neural network nodes in a subject,

determining a second resting functional connectivity of two or more neural network

nodes the subject at a time later than the determination of the first resting functional connectivity of the two or more neural network nodes in the subject, and

comparing the first resting functional connectivity of the two or more neural network nodes to the second resting functional connectivity of the two or more neural network nodes, wherein a difference between the first and second resting functional connectivity of the two or more neural network nodes identifies the onset, progression, or regression of the neurological or psychiatric disease or disorder in the subject.

160. The method of claim 159, wherein a decrease in the second resting functional connectivity of the two or more neural network nodes compared to the first resting functional connectivity of the two or more neural network nodes indicates the onset, progression, or regression of the neurological or psychiatric disease or disorder in the subject.

161. The method of claim 159, wherein an increase in the second resting functional connectivity of the two or more neural network nodes compared to the first resting functional connectivity of the two or more neural network nodes indicates the onset, progression, or regression of the neurological or psychiatric disease or disorder in the subject.

162. The method of claim 159, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, dementia unspecified, multiple sclerosis, depression, anxiety, obsessive compulsive disorder, brain injury, schizophrenia, a sensory neuropathy, a motor neuropathy, a psychotic disorder, migraine, epilepsy, tremor, coma, an affective disorder, stroke, or stroke recovery.

163. The method of claim 162, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease.

164. The method of claim 159, wherein the two or more neural network nodes are located in the left dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), and/or medial frontal cortex (MFC).

165. The method of claim 159, wherein a neural network node is a control neural network node.

166. The method of claim 165, wherein the control neural network node is in the occipitotemporal cortex (OT).

167. The method of claim 159, wherein the method of determining the resting functional connectivity of two or more neural network nodes in the subject comprises obtaining a resting sequence of functional magnetic resonance (fMRI) images of the subject.

168. The method of claim 159, wherein the method of determining the resting functional connectivity of two or more neural network nodes in the subject comprises: collecting data indicative of resting functional connectivity of two or more neural network nodes; and filtering, from the data, a contribution to the data arising from background neural activity.

169. The method of claim 168, wherein the background neural activity comprises neural activity associated with a selected brain region of the subject.

170. The method of claim 169, wherein the selected brain region is a region outside the neural network nodes.

171. The method of claim 159, wherein determining the resting functional connectivity of two or more neural network nodes comprises:

collecting data from the subject during each of a first plurality of intervals, each having at least a first time segment and a second time segment, wherein data is collected from each of the first time segments into a first data set, and data is collected from each of the second time segments into a second data set; and

filtering from the first and second data sets, a contribution to the first and second data sets arising from background neural activity.

172. The method of claim 171, wherein filtering comprises performing a correlation between data representative of the background neural activity and the first and second data sets.

173. The method of claim 171, wherein filtering comprises performing a statistical test

between data representative of the background neural activity and the first and second data sets.

174. The method of claim 159, wherein the subject has been administered a pharmaceutical agent or therapy as a treatment for the neurological or psychiatric disease or disorder.

175. The method of claim 174, wherein the pharmaceutical agent or therapy is administered between the time of the first and second determinations of the resting functional connectivity of the two or more neural network nodes in the subject.

176. The method of claim 174, wherein the pharmaceutical agent is a selective serotonin reuptake inhibitor (SSRI)/antidepressant, a psychostimulant, an N-methyl-D-asparate (NMDA) receptor modulator, an antipsychotic, an anxiolytic, a dopamine/dopaminergic agent, an immune-modulating agent, a cholinesterase inhibitor, or a GABAergic agent.

177. The method of claim 176, wherein the cholinesterase inhibitor is galantamine.

178. The method of claim 174, wherein the therapy comprises application of a medical device or brain surgery.

179. The method of claim 178, wherein the medical device is deep brain stimulation, vagus nerve stimulation, or transcranial magnetic stimulation.

180. A method for identifying a candidate pharmaceutical agent or therapy for preventing or treating a neurological or psychiatric disorder, comprising

determining a first resting functional connectivity of two or more neural network nodes in a subject, wherein the subject has a neurological or psychiatric disease or disorder,

administering a candidate pharmaceutical agent to the subject,

determining after the administration of the candidate pharmaceutical agent or therapy a second resting functional connectivity of the two or more neural network nodes in the subject, and

comparing the first and second resting functional connectivity of the two or more

neural network nodes in the subject, wherein a difference between the first and second resting functional connectivity of the two or more neural networks nodes in the subject identifies the candidate pharmaceutical agent or therapy for preventing or treating the neurological or psychiatric disease or disorder.

181. The method of claim 180, wherein the difference is an increase in the second resting functional connectivity of the two or more neural network nodes in the subject compared to the first resting functional connectivity of the two or more neural network nodes.

182. The method of claim 180, wherein the control resting functional connectivity is a resting functional connectivity previously determined in the subject.

183. The method of claim 180, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, dementia unspecified, multiple sclerosis, depression, anxiety, obsessive compulsive disorder, brain injury, schizophrenia, a sensory neuropathy, a motor neuropathy, a psychotic disorder, migraine, epilepsy, tremor, coma, an affective disorder, stroke, or stroke recovery.

184. The method of claim 183, wherein the neurological or psychiatric disease or disorder is Alzheimer's disease.

185. The method of claim 180, wherein the two or more neural network nodes are located in the left dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), and/or medial frontal cortex (MFC).

186. The method of claim 180, wherein a neural network node is a control neural network node.

187. The method of claim 186, wherein the control neural network node is in the occipitotemporal cortex (OT).

188. The method of claim 180, wherein the method of determining the resting functional connectivity of two or more neural network nodes in the subject comprises obtaining a resting

sequence of functional magnetic resonance (fMRI) images of the subject.

189. The method of claim 180, wherein the method of determining the resting functional connectivity of two or more neural network nodes in the subject comprises: collecting data indicative of resting functional connectivity of two or more neural network nodes; and filtering, from the data, a contribution to the data arising from background neural activity.

190. The method of claim 189, wherein the background neural activity comprises neural activity associated with a selected brain region of the subject.

191. The method of claim 190, wherein the selected brain region is a region outside the neural network nodes.

192. The method of claim 180, wherein determining the resting functional connectivity of two or more neural network nodes comprises:

collecting data from the subject during each of a first plurality of intervals, each having at least a first time segment and a second time segment, wherein data is collected from each of the first time segments into a first data set, and data is collected from each of the second time segments into a second data set; and

filtering from the first and second data sets, a contribution to the first and second data sets arising from background neural activity.

193. The method of claim 192, wherein filtering comprises performing a correlation between data representative of the background neural activity and the first and second data sets.

194. The method of claim 192, wherein filtering comprises performing a statistical test between data representative of the background neural activity and the first and second data sets.

195. The method of claim 180, wherein the candidate pharmaceutical agent is a selective serotonin reuptake inhibitor (SSRI)/antidepressant, a psychostimulant, an N-methyl-D-asparate (NMDA) receptor modulator, an antipsychotic, an anxiolytic, a

dopamine/dopaminergic agent, an immune-modulating agent, a cholinesterase inhibitor, or a GABAergic agent.

196. The method of claim 180, wherein the therapy comprises application of a medical device or brain surgery.

197. The method of claim 196, wherein the medical device is deep brain stimulation, vagus nerve stimulation, or transcranial magnetic stimulation.

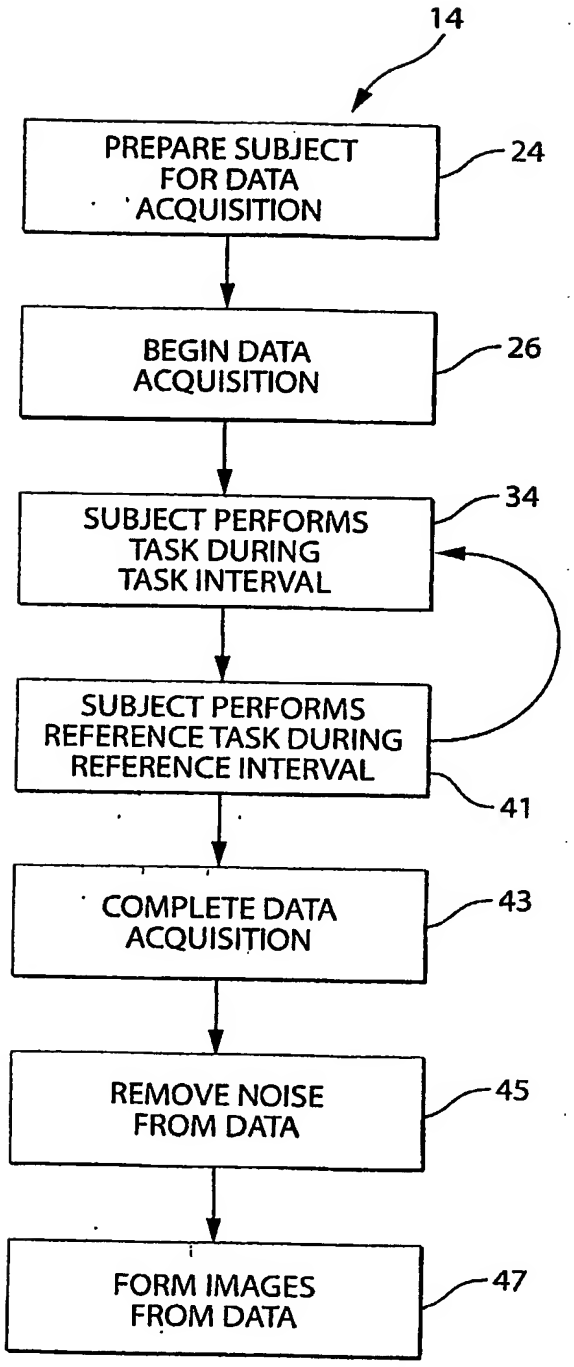

14
PREPARE SUBJECT FOR DATA ACQUISITION
24
BEGIN DATA ACQUISITION
26
SUBJECT PERFORMS TASK DURING TASK INTERVAL
34
SUBJECT PERFORMS REFERENCE TASK DURING REFERENCE INTERVAL
41
COMPLETE DATA ACQUISITION
43
REMOVE NOISE FROM DATA
45
FORM IMAGES FROM DATA
47

Fig. 1

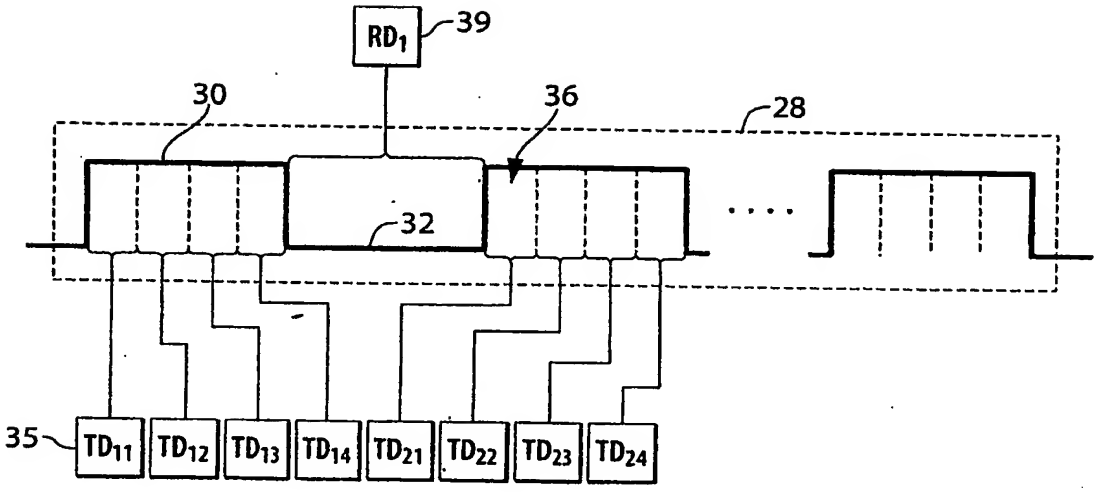


Fig. 2

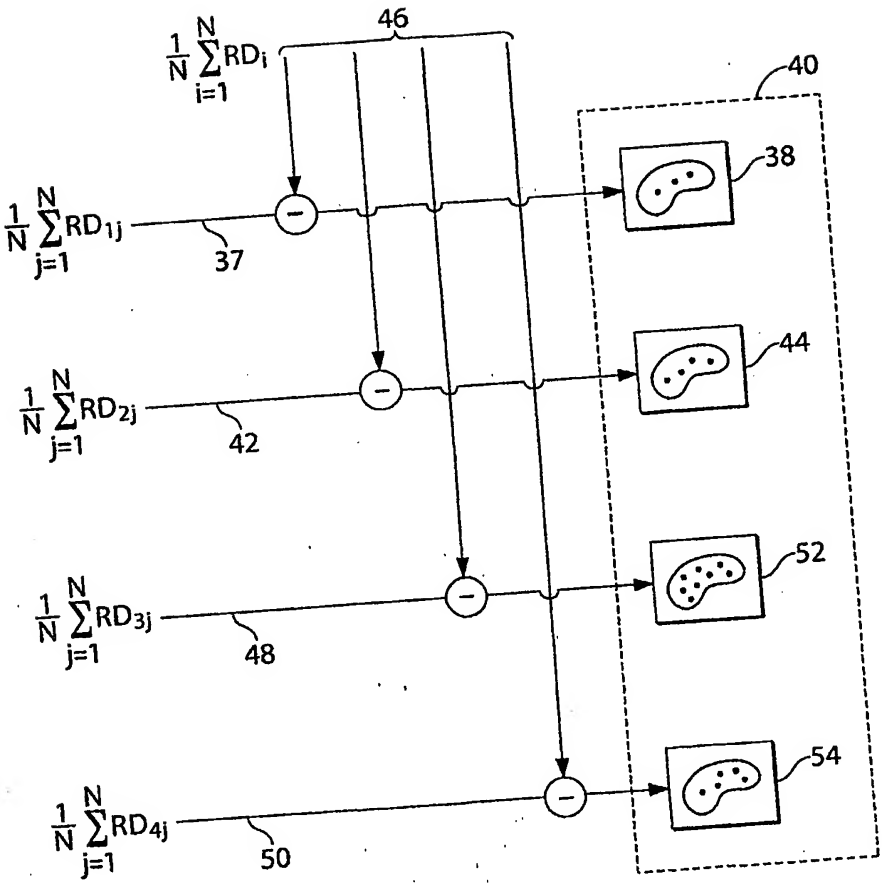

$\frac{1}{N}\sum_{i=1}^{N} RD_i$
46
40
38
$\frac{1}{N}\sum_{j=1}^{N} RD_{1j}$
37
44
$\frac{1}{N}\sum_{j=1}^{N} RD_{2j}$
42
52
$\frac{1}{N}\sum_{j=1}^{N} RD_{3j}$
48
54
$\frac{1}{N}\sum_{j=1}^{N} RD_{4j}$
50

Fig. 3

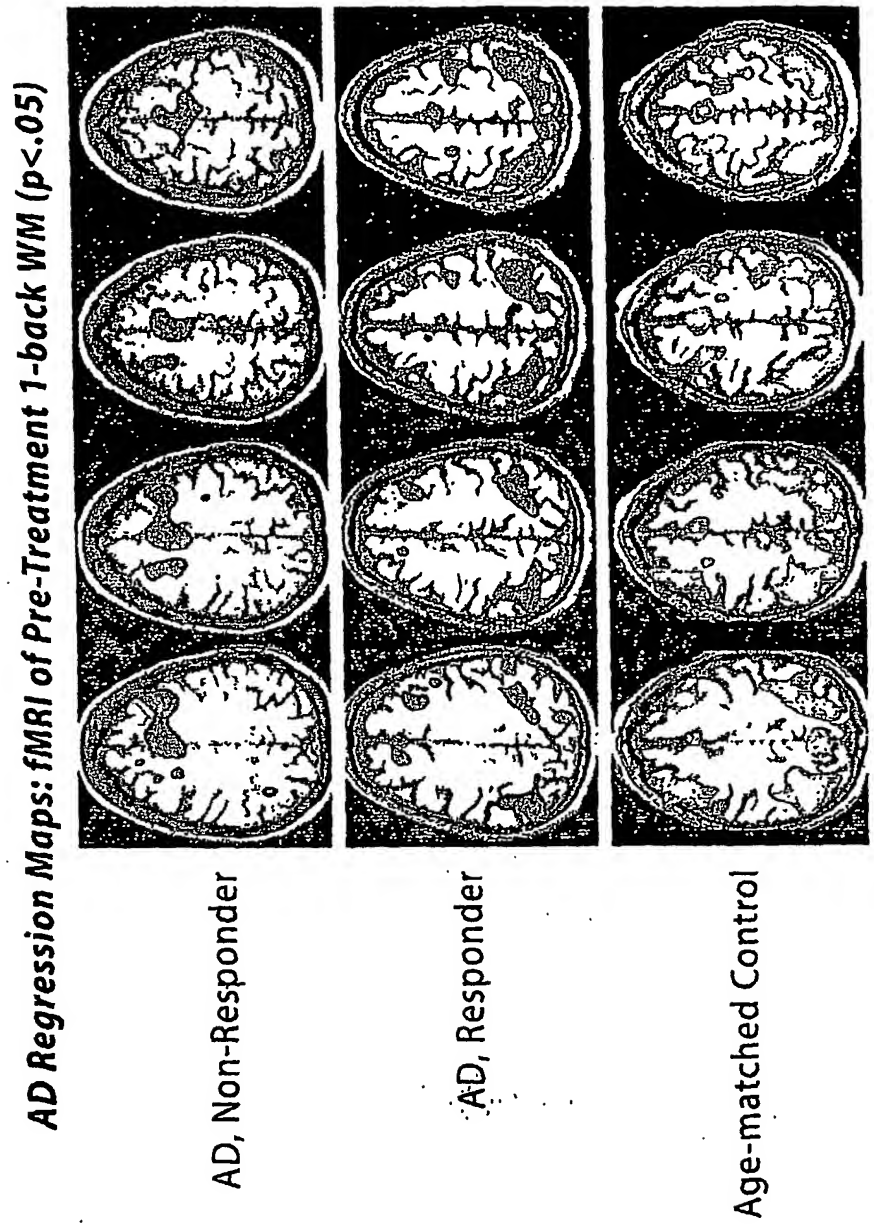
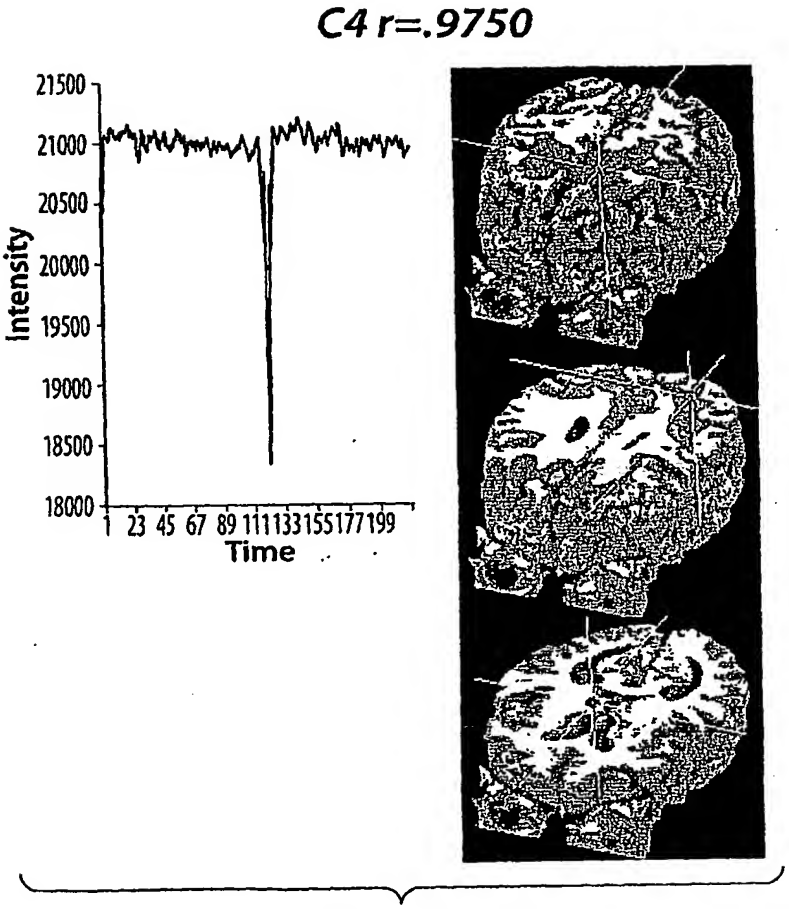

AD Regression Maps: fMRI of Pre-Treatment 1-back WM (p<.05)
AD, Non-Responder
AD, Responder
Age-matched Control

Fig. 4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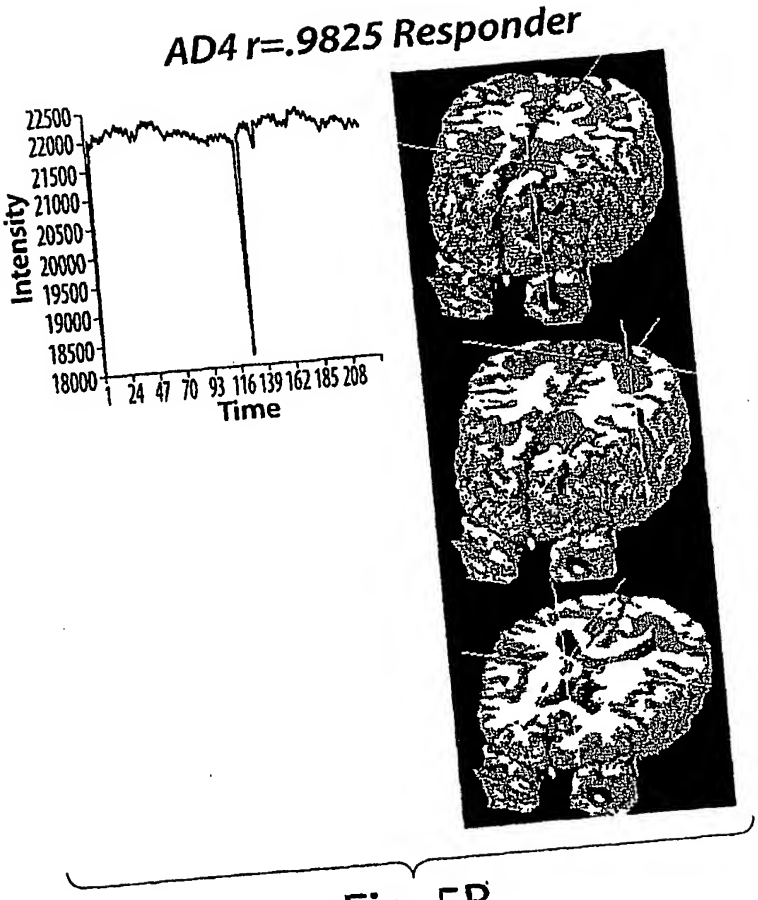
21000
20500
20000
19500
19000
18500
18000
Intensity
1 23 45 67 89 111133155177199
Time

Fig. 5A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20000
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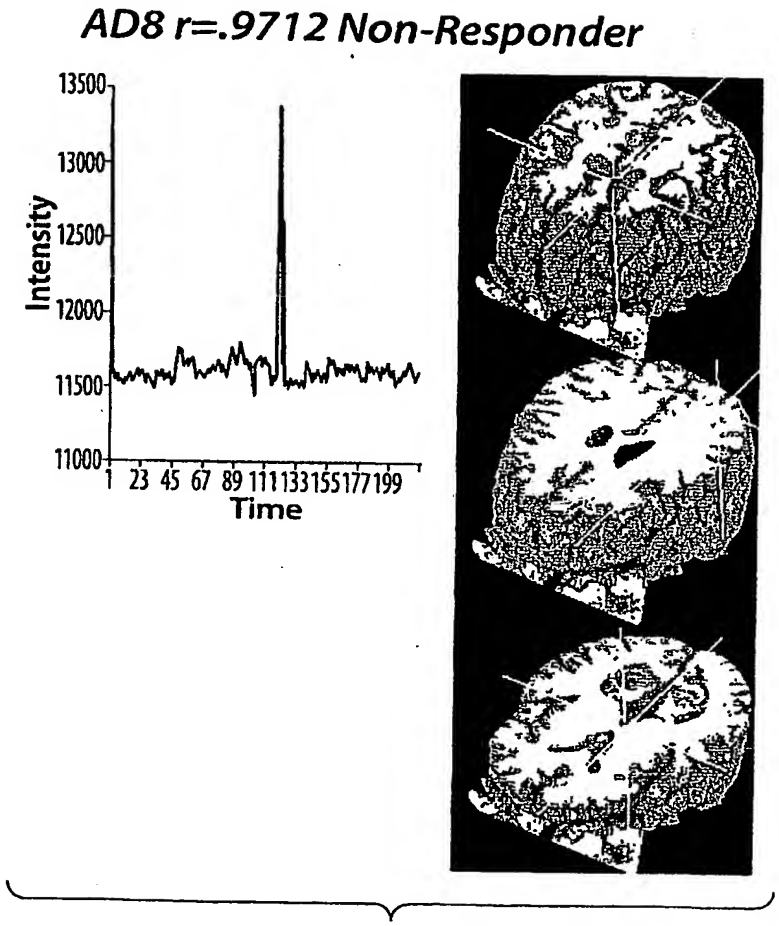
19000
18500
18000
1 24 47 70 93 116 139 162 185 208
Time

Fig. 5B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12500
12000
11500
11000
Intensity
1 23 45 67 89 111133155177199
Time

Fig. 5C

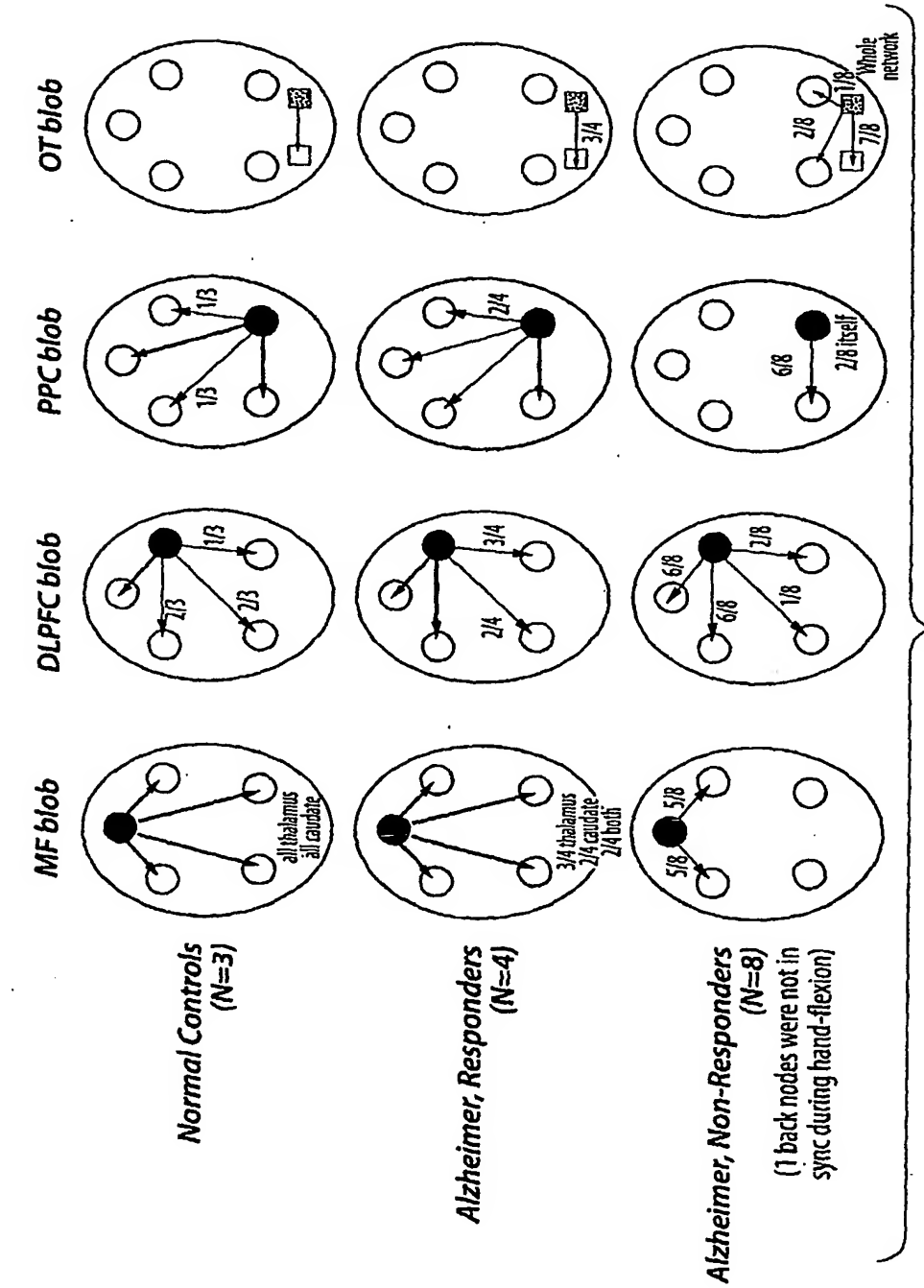
MF blob
DLPFC blob
PPC blob
OT blob
Normal Controls (N=3)
all thalamus all caudate
1/3
2/3
Alzheimer, Responders (N=4)
3/4 thalamus 2/4 caudate 2/4 both
3/4
2/4
Alzheimer, Non-Responders (N=8)
(1 back nodes were not in sync during hand-flexion)
5/8
6/8
2/8 itself
7/8
Whole network

Fig. 6

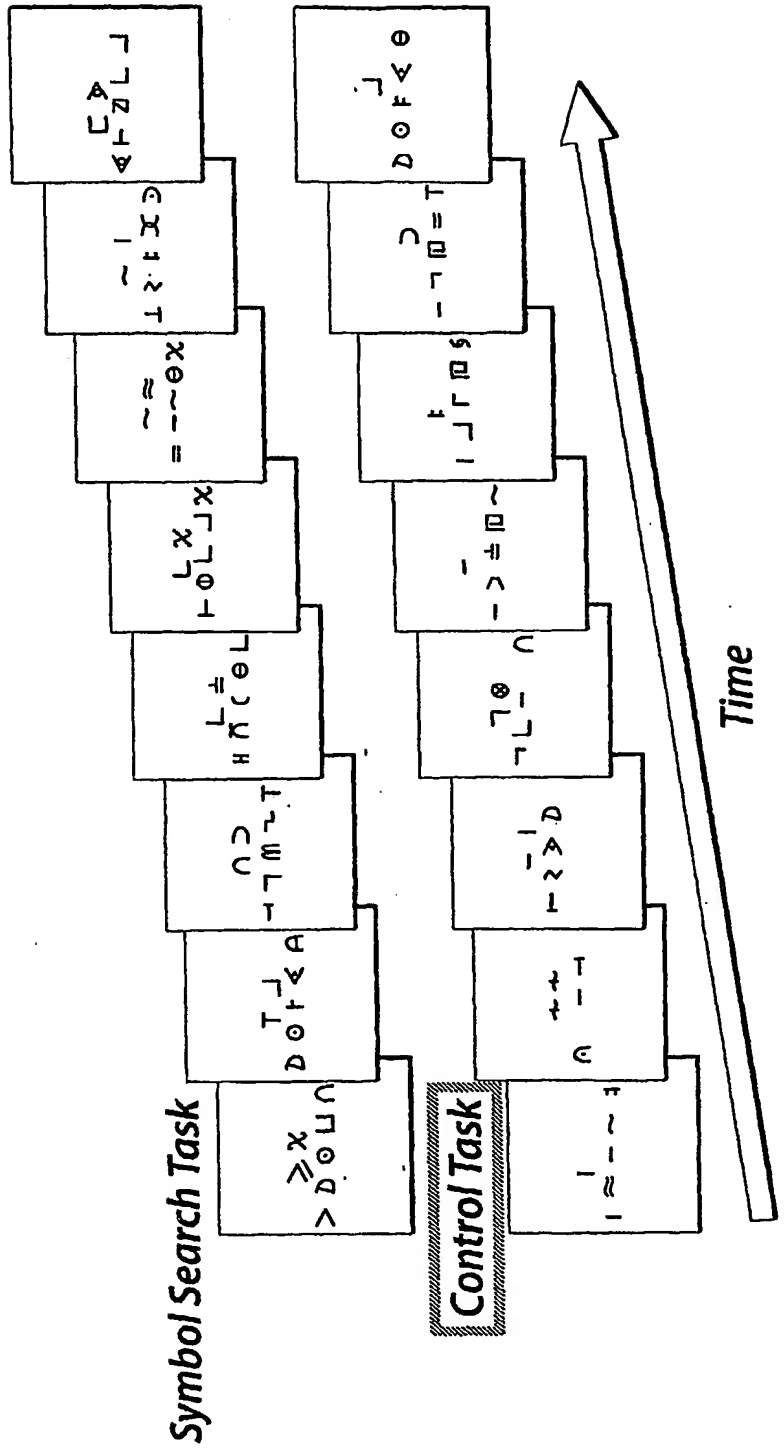

Fig. 7